CYCLOPROPANE ANESTHESIA

Cyclopropane Anesthesia

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To

Berenice Baker Robbins

Preface to the Second Edition

There are many reasons for our desire to prepare a second edition of the monograph Cyclopropane Anesthesia at the present time. During the eighteen years that have elapsed since the first edition, the results of many studies have been reported which help to explain certain of the clinical questions to which there were no satisfactory answers available earlier. Also many studies in the laboratory and in the clinic have been made in an attempt to explain, prevent, or to correct the various cardiac abnormalities that may occur during anesthesia with cyclopropane. We feel that it is desirable to assemble these data in a single text and to present to the student of cyclopropane a unified discussion of the subject.

The apparent increase in the use of cyclopropane in clinical anesthesia as indicated by (1) the writings of several anesthesiologists that cyclopropane should be used more widely, and (2) a statement from one of the leading distributors of anesthetic gases in the United States, that there had been a steady and continuous increase in the use of cyclopropane during the past five years and that the amount distributed by them in 1957 was 50 per cent greater than that in 1953, and (3) a quotation from the report of the division of Synthetic Chemicals of the U. S. Tariff Commission that the sale of cyclopropane had increased from 67,000 pounds in 1951 to 116,000 pounds in 1956, would lead one to the conclusion that a new edition of a monograph was needed.

The introduction of the relaxing agents in 1942 and the widespread use of one of them at the present time make the use of cyclopropane even more satisfactory, in that the lightest planes of

anesthesia are adequate for surgery where the relaxation is provided by another agent.

The general outline of the first edition has been followed very closely in the new one with major changes in the text of all but three chapters and the addition of a chapter upon the relaxing agents. The greatest changes have been made in Chapters 2, 3, 4, and 8.

The present edition retains thirty-six of the old figures to which thirty-eight new ones are added; thirty-nine of the old tables with fifteen new ones added; and the present bibliography includes about one hundred, seventy-five new titles of the more significant reports that have been made since 1939.

I am indebted to many individuals for help in the preparation of this monograph, particularly to my associate Dr. Lawrence G. Schull for his assistance in carrying an excessive share of my teaching load during the past three months, to members of our Department of Illustration, to our library staff, and especially to my efficient and cooperative secretary, Mrs. Arthur Briggs, for her patience in the preparation of the manuscript. My thanks are due the publishers, The Williams and Wilkins Company, for their cooperation in accepting the manuscript and preparation of the book.

BENJAMIN HOWARD ROBBINS, M.D.

Nashville, Tennessee
March 12, 1958

Foreword to First Edition

The world owes more, perhaps, than it realizes to Dr. Velyien E. Henderson, who, after years of work on anesthesia, in 1928 discovered with Dr. G. H. W. Lucas the anesthetic properties of the gas cyclopropane. This discovery by Dr. Henderson and Dr. Lucas is one of the most satisfactory examples of modern pharmacology. These workers were led by their experiments to investigate cyclopropane, which at that time was a mere curiosity of the chemical laboratory. They themselves synthesized this gas, purified it, proved its anesthetic properties on animals, determined quantitatively the amount necessary for anesthesia, and then carried out a sufficiently diversified series of animal experiments to demonstrate its probable safety; but before turning this gas over to the medical profession for clinical trial, they anesthetized each other and determined quantitatively the amount necessary for anesthesia on themselves.

In the short space of ten years which has elapsed since then, cyclopropane has been used in some two hundred and fifty thousand clinical ansethesias with very great success. Clinicians, as well as laboratory workers, have studied the reaction of the human organism to this gas from about every angle. The medical investigators are not, however, the only ones who have been busy; chemists and chemical manufacturers have devised new methods for its production and purification, and it now can be obtained in any amount at approximately one-twelfth its cost in 1934.

This book by Dr. Robbins will not only serve to bring together the facts about cyclopropane but will give a much-needed evaluation of the large amount of literature which has already accumulated. A glance at the text will be sufficient to show the interest of the author in quantitative procedures, which are the basis for a true understanding of the behavior of any drug. We owe much to Dr. Robbins for his own contributions to our knowledge of cyclopropane. It was he who first devised a method for quantitating this gas in the blood, which was essential for an understand-

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ing of its action. We are also indebted to him for his explanation of the occurrence of cardiac irregularities which have been seen altogether too often after the use of cyclopropane in the clinic and which have caused no little fear as to the safety of the drug. He has shown in animals that cyclopropane alone causes no cardiac irregularities in dogs in all reasonable depths of anesthesia, that morphine alone in therapeutic doses also causes no cardiac irregularities, but that if morphine is followed by cyclopropane, cardiac irregularities similar to those observed in the clinic immediately appear. As morphine is used for premedication in almost all clinical anesthesias with cyclopropane, this might account for the appearance of cardiac irregularities attributed to cyclopropane itself. Dr. Robbins has found that barbiturates not only can be used as preanesthetic agents with cyclopropane without the appearance of cardiac disturbances but that they will prevent the morphine-cyclopropane irregularities. It is to be hoped that his findings may apply in man and that the substitution of a barbiturate for morphine as a premedication agent in cyclopropane anesthesia will remove the last contraindication to what may be considered some day the most perfect of all gaseous anesthetics.

PAUL DUDLEY LAMSON

Nashville, Tennessee
November 23, 1939

Acknowledgment from First Edition

My thanks are due to many—to Dr. P. D. Lamson, for his interest in and criticism of our experimental studies during the past three years; to Mr. J. H. Baxter, Jr., Dr. O. G. Fitzhugh, and Dr. William Govier, for their aid in the experimental studies; and to Mr. Edward Mallinkrodt, Jr., for the many manifestations of his interest in the advancement of anesthesia.

BENJAMIN HOWARD ROBBINS

Nashville, Tennessee
November 23, 1939

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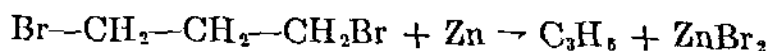
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Physical and Chemical Properties of Cyclopropane

METHODS OF PREPARATION

Cyclopropane, or trimethylene, is the simplest of the cyclic hydrocarbons. Freund (105) in 1882 was the first to prepare and identify this compound; he made it by reducing trimethylene dibromide with sodium in an alcoholic solution. Propylene, $CH_3—CH=CH_2$, an isomer of cyclopropane, was the only impurity that he mentioned as being present in the effluent gas from the reaction. During the next twenty years several methods for the preparation of cyclopropane were advanced, but no method was as satisfactory as the procedure of Freund.

Lott and Christiansen, 1930, (189) reviewed the earlier literature on the synthesis of cyclopropane and described the method they employed in the preparation of cyclopropane in relatively large amounts. It was similar to that of Freund. They used ethyl alcohol (about 87 per cent conc.) as a solvent, zinc dust as the reducing agent, and gradually introduced trimethylene dibromide while stirring the mixture and obtained an effluent gas which was 99.5 to 100 per cent absorbable in concentrated H_2SO_4; it showed no propylene when treated with acid $KBrO_3$. Their yield in laboratory runs was as high as 80 per cent of the theoretical. Two of the manufacturers of cyclopropane for anesthesia, Ohio Chemical Company and Squibb, use the procedure for preparing their cyclopropane (71). The reaction is as follows:



$$Br—CH_2—CH_2—CH_2Br + Zn \rightarrow C_3H_6 + ZnBr_2$$

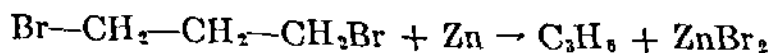
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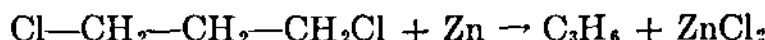
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In 1936, Haas, McBee, Hinds, and Glusenkamp (137) reported the production of cyclopropane from the reduction of 1,3-di-

chloropropane by zinc dust; Gustavson (135) had reported a similar method, but the yield was much lower than that obtained when 1,3-dibrompropane was used. The method of Haas *et al.* has been used by the Mallinckrodt Chemical Works for the production of cyclopropane for anesthesia (138).



$$Cl—CH_2—CH_2—CH_2Cl + Zn \rightarrow C_3H_6 + ZnCl_2$$

PHYSICAL CHARACTERISTICS

Boiling point: −32.89°C. (137); −32.2°C. (71).
Freezing point: −126°C. (137); −127°C. (71).
Density in relation to air: 1.46 S.T.P.
Molecular weight: 42.1

CHEMICAL CHARACTERISTICS

Cyclopropane is relatively inert chemically; Roginski (282) showed that it does not react readily with iodine or bromine to form addition products; neither is it oxidized by permanganate or acid chromate to any appreciable extent. It is, however, readily absorbed by concentrated sulfuric acid, and this property is one that has been made use of in the quantitative studies by various investigators (146, 210, 272).

SOLUBILITY OF CYCLOPROPANE IN WATER, BLOOD, AND OILS

Several investigators, using different methods, have determined the solubility of cyclopropane in water, blood, and oils.

Water. Lucas and Henderson (190) first reported that water absorbed 16.5 volumes per cent of cyclopropane from an atmosphere of cyclopropane at 35°C. Robbins (272), using the iodine pentoxide method for the determination of cyclopropane, found the Ostwald constant or distribution ratio of cyclopropane between the gas and water phase to be .281 at 25°C.; and Orcutt and Seevers (239), using their modification of the Van Slyke-Neill manometer technic, obtained an Ostwald constant of .278 at 25°C. Killian (167) found the solubility of cyclopropane in water to be

.296 at 20°C. by saturation, which is near the value of .315 at 20°C. obtained by Robbins (272).

Blood. Robbins (272) reported the solubility in blood to be .47 to .51 at 38°C., and Orcutt and Seevers (239) obtained a value of .457 at 37.5°C. Killian (167) found it to be .503 in defibrinated ox blood at 20°C. More complete data will be given in table form below.

Oils. Lucas and Henderson reported the solubility in olive oil to be 10.3 at 35°C., and Orcutt and Seevers found the solubility to be 6.99 at 37.5°C.

METHODS USED FOR DETERMINING THE AMOUNT OF CYCLOPROPANE IN THE GAS SAMPLES, WATER, AND BLOOD

Gas samples. The absorption of cyclopropane by concentrated H_2SO_4 is the most rapid method available. Any standard gas analysis apparatus can be adapted for this use by adding an absorption bottle containing concentrated H_2SO_4. Robbins (272) and Meek, Hathaway, and Orth (210) used this method on an Orsat-Henderson apparatus; Seevers *et al.* (297) used a Burrell apparatus in their studies.

Blood and water samples. Orcutt and Seevers (239) used the Van Slyke-Neill manometric method for determining the solubility of cyclopropane in water, oils, and human blood.

The iodine pentoxide oxidation method can be used for the determination of cyclopropane in water or blood samples, provided there is no other volatile organic substance present. This method has been very satisfactory in our studies, and since it is not so widely known as the Van Slyke-Neill procedure, it will be described in some detail. It was first used by Teague (328) for the determination of carbon monoxide; later by Haggard for ether (139) and by Haggard and Greenberg for alcohol (140). The procedure, as we used it for the determination of cyclopropane in air, water, and blood samples, is described in detail below. A diagrammatic drawing of the oxidation train is shown in figure 1.

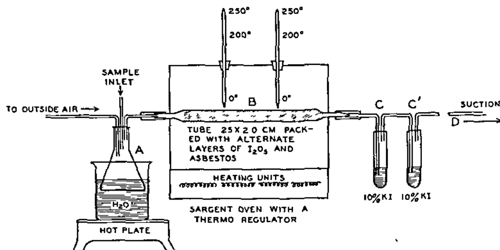


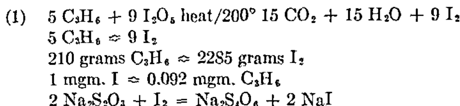
Fig 1. Iodine pentoxide train used for the determination of cyclopropane in air, water, and blood. (Robbins· Anesth & Analg , **16**, 93, 1937).

The oxidation train consists of the following: A, an Erlenmeyer flask of 125 cc. capacity which is closed with a stopper pierced by three tubes, one for intake of outside air (free of organic matter), a second for introduction of the sample to be analyzed, and a third for carrying the air and cyclopropane to tube B, a pyrex tube 25 by 2 cm packed with alternate layers of iodine pentoxide (a total of 45 to 50 grams) and asbestos (freed of organic matter by boiling in acid chromate and then washing). Tube B is contained in a small Sargent oven which is kept at a temperature of 205° to 210°C. From B the train connects to two large test tubes, C and C′, in series each containing 25 cc. of 10 per cent potassium iodide for the collection of the liberated iodine. D, or the suction line, connects to either tube C′ or B depending on whether one is making a determination or not. About five hundred samples of 2 to 7 mgm. each have been oxidized by the iodine pentoxide in one tube.

Procedure of analysis. The oven is brought to 200° while air is being drawn at the rate of 150 to 200 cc. per minute, through the train. The tubes C and C′ are then placed in line. A measured volume of the unknown sample of water or blood is introduced

at one time into flask A, or for an air sample the introduction is gradual over a period of five minutes. The water or blood containing flask is gently shaken for five minutes after which it is surrounded with a boiling water bath and heated for five minutes more. Then fresh tubes C and C′ are placed in line and another collection made for five minutes. Usually the second set of tubes contains no more iodine than liberated by a blank analysis. The liberated iodine is titrated against a standard thiosulfate solution of about 0.02 N.

Equations and calculations. The equations for the oxidation and titration are as follows:



(1) $5\ C_3H_6 + 9\ I_2O_5 \text{ heat/200° } 15\ CO_2 + 15\ H_2O + 9\ I_2$

$5\ C_3H_6 \approx 9\ I_2$

$210 \text{ grams } C_3H_6 \approx 2285 \text{ grams } I_2$

$1 \text{ mgm. } I \approx 0.092 \text{ mgm. } C_3H_6$

$2\ Na_2S_2O_3 + I_2 = Na_2S_4O_6 + 2\ NaI$

The equation I is for the maximum oxidation of cyclopropane and maximum liberation of iodine. We feel that it correctly represents the reaction because, when air samples of known cyclopropane content are oxidized, the iodine liberated is 98 to 100 per cent of the calculated amount. Also, if the iodine is driven off from tube C by heat and passage of air, the residual fluid fails to give a positive test for hydrogen iodide when potassium iodate and acid are added.

Analysis of air-cyclopropane mixtures by iodine pentoxide. Varying mixtures of unknown concentrations of air and cyclopropane were made in a 20-liter bottle. The concentration of cyclopropane in a dry, carbon dioxide-free mixture was determined by use of a standard Orsat-Henderson apparatus in which concentrated sulfuric acid was the absorbing agent and mercury the displacing agent. Five or six washings over the concentrated sulfuric acid removed all of the cyclopropane present. A 14 cc. sample was then taken from the bottle over mercury and gradually introduced into flask A of the oxidation train. At the end of ten

minutes the potassium iodide-iodine containing tubes, C and C′, were emptied into a flask, rinsed, and the mixtures titrated against $Na_2S_2O_3$. A sample calculation is given below:

> Orsat-Henderson analysis gave a 13 4 volume per cent concentration.
> 14 cc sample at 30° was taken for analysis by I_2O_5 train.
> 1 cc. C_3H_6 at 760 mm. and 30° weighs 1.68 mgm.
> ∴ 14 cc. × 13.4 × 1 68 = 3 15 mgm. sample of C_3H_6.
> Iodine pentoxide analysis:
> 2 65 cc. of N/10 $Na_2S_2O_3$ were required to titrate the liberated iodine.
> 1 cc N/10 $Na_2S_2O_3$ ≎ 1.17 mgm. C_3H_6
> ∴ 2.65 × 1 17 = 3 10 mgm by I_2O_5 oxidation.
> 3.1/3 15 × 100 = 98.4 per cent recovery.

By a similar procedure 23 other samples of gas containing from 2.8 to 7.2 mgm. were analyzed by the Orsat-Henderson apparatus and iodine pentoxide train. The results are given in table 1.

The recovery by the iodine pentoxide train varied from 98 to 101.5 per cent with an average of 99 per cent. One can, therefore, consider the iodine pentoxide method accurate for the determination of cyclopropane in samples containing as much as 7 mgm.

TABLE 1*

Analysis of air-cyclopropane mixtures by Orsat-Henderson and iodine pentoxide methods

Orsat-Henderson—C_3H_6	I_2O_5 Method—C_3H_6	Orsat Henderson—C_3H_6	I_2O_5 Method—C_3H_6
mgm	*mgm*	*mgm*	*mgm*
3 15	3 10	7 02	6 88
3 08	3.05	6.95	6 80
2 91	2 89	6.82	6.67
2 89	2 86	6 78	6 67
2 87	2 86	4 82	4 80
2 82	2.81	4.75	4.70
2 80	2 81	4.72	4.70
5 38	5 28	4.66	4.64
5 34	5 24	4 64	4 62
5.30	5 26	4.57	4.61
5.25	5 16	6 60	6.70
5 15	5.12	6.57	6 50

* Robbins: J Pharmacol and Exper Therap, 58, 243, 1936 (272).

Solubility of cyclopropane in water. We have determined the solubility over a temperature range of 20° to 45°C. Pure cyclopropane (Ohio Chemical) was bubbled for one to two hours through a cylinder of water immersed in a water bath kept at constant temperature. After continuous passage of cyclopropane through the water, 10 cc. samples of water were analyzed for their cyclopropane content. The procedure was the same as that for air except the samples were taken in a calibrated syringe which had been immersed in the water bath so as to be of the same temperature as the sample for analysis. The concentration of cyclopropane in the space over the water was not analyzed but calculated; we considered it to be pure gas diluted with water vapor at the temperature of the bath.

Three or more determinations were made at each of the following temperatures: 20°, 25°, 30°, 31°, 35°, 39°, and 45°. The results of these determinations are recorded in table 2 and figure 2. By looking at the table it can be observed that at 35°C. water equilibrated with pure cyclopropane contains not 16 cc. of gas per 100 cc., as found by Henderson and Lucas (146), but 20.8 cc. This difference may be due to one of two factors: first, that the gas studied by Henderson and Lucas, as they suggest, was not pure; and second, that they may have failed to consider the volume occupied by water vapor at 35°C.

Solubility of cyclopropane in blood. The blood samples were equilibrated with the cyclopropane-oxygen mixtures by use of a cylindrical pyrex tonometer. Five cubic centimeter samples of gas and blood were analyzed for their *cyclopropane content after* equilibration.

Samples of blood (oxalted) from two dogs, as well as samples from two men, were equilibrated with cyclopropane over a temperature range from 20° to 40°C. The results of these studies are shown in table 3 and figure 2. The distribution ratios for the different samples are not the same. This difference in the distribution ratio may be due in part to the variation in fat content of the blood samples from different dogs and men, because the solubility

TABLE 2*

Distribution coefficient of cyclopropane between water and air—Equilibrated by bubbling pure gas 100 per cent through water

Temperature	Cyclopropane			D.C. $\frac{\text{Water}}{\text{Air}}$
	Water		Air	
°C.	mgm per 100 cc		mgm per 100 cc	
20	54.0.			
	54.0.	53.9	171.0	0.315
	53.7.			
25	46.2.			
	46.7.	46.4	165.0	0.281
	46.2.			
30	39.2			
	38.9.	39.2	161.5	0.243
	39.4			
31	38.3.			
	37.8	37.8	160.0	0.236
	37.8.			
	37.3			
35	32.7			
	33.0	32.5	156.5	0.208
	31.8			
39	28.9			
	28.1.	28.8	152.0	0.189
	29.2			
	29.2			
45	24.8.			
	25.1	24.9	149.0	0.167
	24.8			

* Robbins J Pharmacol. and Exper Therap., 58, 243, 1936 (272).

of cyclopropane in fat is about twenty times greater than in blood. In order to show that the fat content does alter the solubility in blood, the following experiments were carried out:

Fifty cubic centimeter samples of blood were drawn from two dogs. Immediately following the taking of the blood, each dog was given 400 cc. of 20 per cent cream by stomach tube. Three hours after the fat meal, second 50 cc. samples of blood were taken. Five cubic centimeters of each sample were centrifugalized, and,

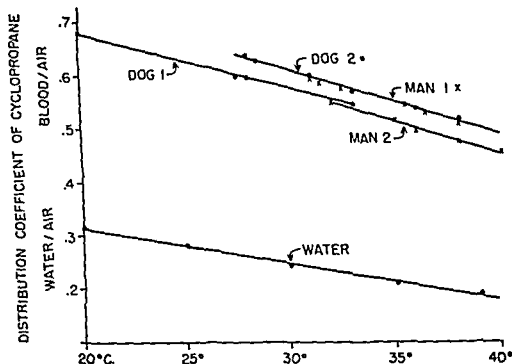


FIG 2 Distribution coefficient of cyclopropane between water and air and blood and air. From data in tables 2 and 3 (Robbins (272))

whereas the plasma of the first samples was clear, the plasma of those taken after the cream meal was very turbid. The distribution ratios for these normal and fat containing samples were determined in duplicate or triplicate at 34°C. In experiment 1 the distribution ratio was 0.565 before the fat meal and 0.588 three hours after. In experiment 2 the ratio at 34° was 0.551 before the fat meal and 0.611 after the meal.

A second and more probable factor in the variation of the distribution ratio observed in blood from different dogs and men is the difference in plasma-cell ratio Grollman (128) has shown that the solubility of ethylene in blood samples varied with changes in the plasma-cell ratio.

In three samples of blood from dogs the distribution ratios in the whole blood and plasma were determined; the values for the

TABLE 3*

Distribution coefficient of cyclopropane between blood and air—Equilibrated by rotation of cylinder with 250 cc gas, 6 cc. blood

BOTH GAS AND BLOOD SAMPLES ANALYZED BY I_2O_5 METHOD (5 CC. SAMPLE OF EACH)

Subject	Temperature	Cyclopropane		D C $\frac{\text{Blood}}{\text{Air}}$
		Blood	Air	
	°C	mgm per 100 cc	mgm per 100 cc	
Dog 1	20 0	107.0	156.6	0.685
	20.0	105.4	155 6	0.680
	20 0	105.4	156 6	0.675
	27.5	48 4	81.0	0.597
	28 0	52.6	88.4	0.595
	28.0	42.6	72.0	0.592
	28 0	41 0	68.8	0.595
	28.5	42.6	74.2	0.575
	33.0	35 0	61.0	0 547
	33.0	31.0	58 4	0.532
Dog 2	28.0	61.6	97.4	0.632
	28 5	61.6	99.4	0 620
	28 5	56.8	90 0	0.630
	31 0	56.8	95 6	0 594
	33 0	40.4	71.4	0.566
	36 0	51 6	98.0	0.527
	36 0	44.6	83.0	0 537
	38 0	49.0	95 2	0.513
Man 1 (1 hour after lunch)	31 0	26 3	44.6	0.591
	31 5	36 2	61.0	0.593
	31 5	29 4	51.4	0.572
	32 5	35 8	63.0	0.570
	32 5	22 5	39.4	0.573
	35 5	31.6	58.4	0 540
	36 0	22 1	41.0	0.540
	36 5	31.6	60 0	0.527
	38 0	30 0	59 0	0.508
Man 2 (4 hours after breakfast)	32 0	44 6	82.0	0 545
	32 0	44 0	80 0	0 550
	35 0	40 8	80.0	0.510
	36 0	39 5	80.4	0 492
	38 0	36 8	78 4	0.470
	40 0	35.6	78.8	0 451

* Robbins. J Pharmacol and Exper Therap , 58, 243, 1936 (272).

plasma samples at 34°C. were 0.327, 0.320, and 0.324; the corresponding values for whole blood were 0.562, 0.482, and 0.502; the cell volumes were 45 per cent, 34.5 per cent, and 39 per cent, respectively. By calculation, then, the distribution ratios in the cells were 0.847, 0.780, and 0.785. Thus the solubility of cyclopropane in the cells is about two and one-half times that in the plasma. Therefore, a relatively small change in total cell volume would account for the variations observed in whole blood.

Possati and Faulconer (257) have made careful studies on the effect of the hemoglobin concentration on the distribution ratio of cyclopropane between human blood and air in vitro. They started with blood containing 15 grams of hemoglobin per 100 cc. and diluted it stepwise with plasma from the same subject to 3 grams of hemoglobin per 100 cc. and determined the distribution ratio using the mass spectrometer for the cyclopropane analyses and obtained the values which are shown in figure 3. At thirty-seven degrees and 15 grams of hemoglobin per 100 cc. the distribution ratio was .415 which is reasonably close to the values of .457 and .451 reported by Orcutt and Seevers (239) and Robbins (272), respectively. If one assumes a cell volume of three per cent per 1 gram of hemoglobin and calculates the solubility in the red cells from the data of Possati and Faulconer, one finds the solubility in the red cells to be about 2.3 times as great as it is in the plasma. This value is very near 2.5 which was observed by Robbins (272).

Killian (167), by calculation, using the solubility of cyclopropane in whole blood and the oil/water ratio, states the plasma contains 57 per cent and the cells 43 per cent of the cyclopropane in the equilibrated blood.

Seevers and Waters (298) have reviewed the literature on the solubility of cyclopropane in water, blood, and oils. Table 4 is taken from their paper.

TESTS FOR PURITY OF CYCLOPROPANE

Burger (49), 1937, reported the results of his investigation of the three brands of cyclopropane available in the United States

TABLE 3*

Distribution coefficient of cyclopropane between blood and air—Equilibrated by rotation of cylinder with 250 cc. gas, 6 cc. blood

BOTH GAS AND BLOOD SAMPLES ANALYZED BY I_2O_5 METHOD (5 CC. SAMPLE OF EACH)

Subject	Temperature	Cyclopropane		D.C. Blood/Air
		Blood	Air	
	°C.	mgm per 100 cc	mgm. per 100 cc	
Dog 1	20 0	107 0	156.6	0.685
	20 0	105.4	155.6	0.680
	20 0	105 4	156.6	0.675
	27.5	48 4	81.0	0.597
	28.0	52.6	88.4	0.595
	28 0	42.6	72 0	0.592
	28 0	41.0	68.8	0 595
	28.5	42.6	74.2	0.575
	33.0	35 0	64.0	0.547
	33.0	31.0	58.4	0.532
Dog 2	28.0	61 6	97.4	0 632
	28.5	61.6	99.4	0.620
	28 5	56.8	90 0	0.630
	31.0	56.8	95 6	0.594
	33 0	40.4	71.4	0.566
	36 0	51.6	98.0	0.527
	36 0	44.6	83.0	0 537
	38 0	49 0	95.2	0.513
Man 1 (1 hour after lunch)	31 0	26 3	44 6	0.591
	31 5	36 2	61.0	0.593
	31 5	29 4	51.4	0.572
	32 5	35 8	63 0	0.570
	32 5	22 5	39 4	0.573
	35 5	31 6	58 4	0.540
	36 0	22.1	41.0	0.540
	36 5	31 6	60.0	0.527
	38 0	30 0	59 0	0 508
Man 2 (4 hours after breakfast)	32 0	44 6	82 0	0.545
	32 0	44 0	80.0	0.550
	35 0	40 8	80 0	0.510
	36 0	39 5	80.4	0 492
	38 0	36 8	78 4	0 470
	40 0	35 6	78 8	0.451

* Robbins. J Pharmacol and Exper Therap , 58, 243, 1936 (272).

TABLE 4*

The solubilities of pure cyclopropane as determined by saturation (167), extraction (239), and iodine pentoxide (272)

Temperature	Water		Blood		Oil
	λ		λ		λ
20	.315 (272)	.296 (167)	.680 (272)	.503 (167)	11.14 (167)
25	.281 (272)	.278 (239)			9.79 (239)
37 5		.204 (239)		.457 (239)	6.99 (239)
39		.181 (272)		.451 (272)	

λ = Ostwald solubility expression, or the volume of gas dissolved by unit volume of solvent at a given temperature for any pressure, when the pressure of the gas itself minus the vapor tension of the solvent is equal to atmospheric pressure

* Seevers and Waters: Physiol. Rev., 18, 447, 1938 (298).

There was no significant difference in the quantity of propylene as determined by the two methods.

There was never a positive test for halides obtained on any of these brands.

Although Burger thought that cyclohexane might be formed in the preparation of cyclopropane, it seems very doubtful that it would be present in detectable amounts in anesthetic cyclopropane because cyclohexane boils at +80°C. whereas cyclopropane boils at −32.89°C.

EXPLOSIVE HAZARDS

Buckman and Wardell (44) have determined the concentrations of cyclopropane in air and in oxygen which are explosive and presented these data together with similar data for ether and ethylene (table 5).

More complete data on several anesthetic agents have been reported by G. W. Jones (161), Bureau of Mines, Investigation No. 3443 (table 6).

The problem of explosive hazards with cyclopropane is of such importance that several studies have been made on ways of reducing them. One major report of the Council on Pharmacy and Chemistry of the A.M.A. (72) deals with this subject. Thomas

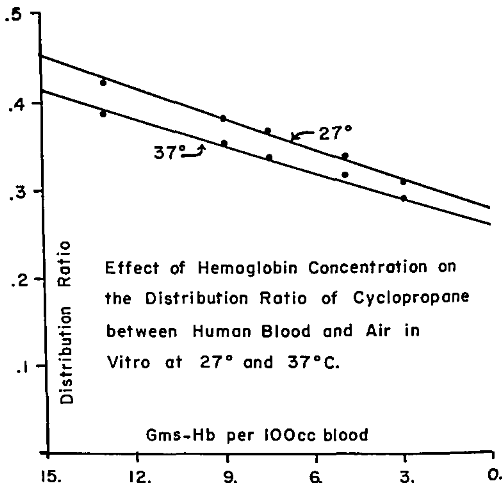


FIG 3 Drawn from data of Possati and Faulconer (257))

at that time. Two of them were prepared from 1,3-dibrompropane and the other from 1,3-dichloropropane. A study of the synthetic processes used in the preparation from the dihalides of propane led him to believe that propylene, cyclohexane and halogen compounds would be the more probable contaminants. He used $KMnO_4$ and iodine to determine the presence and quantity of unsaturated hydrocarbons and calculated these as propylene. The results obtained are shown below.

	Per cent Propylene	
	O_2 uptake	I_2 uptake
Brand A	2.85	2 8
Brand B	2 56	2 5
Brand C	.12	.14

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Temperature	Water		Blood		Oil
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37.5		.204 (239)		.457 (239)	6.99 (239)
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λ = Ostwald solubility expression, or the volume of gas dissolved by unit volume of solvent at a given temperature for any pressure, when the pressure of the gas itself minus the vapor tension of the solvent is equal to atmospheric pressure.

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Further discussion of explosive hazards and records of cases will be given in Chapter 12, but it is desirable to call attention to two facts shown in table 6; first, all anesthetics except N_2O and $CHCl_3$ are explosive in anesthetic concentrations; second, ether has a much lower ignition temperature than either C_2H_4 or C_3H_6, which offer greater hazards in the operating room.

SUMMARY

The present methods of production of cyclopropane for anesthesia are based upon the original observation of Freund that the 1,3-dihalide of propane, when added to a solution containing elemental metal—sodium, zinc, or magnesium, will react to form cyclopropane.

Cyclopropane is a gas at room temperature, with a boiling point of −32.89°C. at atmospheric pressure. It has a density of 1.46 in relation to air.

The distribution coefficient at 37.5°C. for water is .204, for blood .457 to .49. It is about two and one-half times more soluble in the cells than in the plasma.

The gas is rapidly absorbed by concentrated sulfuric acid and is readily oxidized by iodine pentoxide.

2

The Concentrations of Cyclopropane Required for the Different Levels of Anesthesia and for Respiratory Arrest

Until 1920, the transition from the awakened state to that of respiratory arrest had been divided into four stages. (1) Stage of analgesia. (2) Stage of delirium and excitement. (3) Stage of surgical anesthesia. (4) Stage of respiratory arrest.

In 1920, Guedel (130) published a paper dividing the stage III of surgical anesthesia into four different planes using changes of various signs as guide posts to identify these different planes. Of particular value in this study was the change in the movement of the eyeball and the size of the pupil. Also the alteration in the respiratory rate and the curves subscribed by the respiratory cycle, and finally the relaxation of skeletal muscle. This classification of Guedel has been used from 1920 up until 1950 and in most places to the present with modification of special points by different people during the past 30 to 35 years.

In 1950, Courtin, Faulconer, and Bickford (74), making use of electroencephalographic equipment, described the transition from the awakened conscious state to that of respiratory arrest under anesthesia and divided this into seven different planes. In many places at the present time, the electroencephalograph is an instrument of great use in determining the depth of anesthesia of patients in the operating room. It has also been used at different places, particularly at the Mayo Clinic and at the Cornell Hospital, as an aid in the maintenance of anesthesia at a fixed level.

Another method of determining the depth of anesthesia that might be developed is that investigated by Rence, Cullen, and Hamilton (264) in which cathode ray tracings were made of the heart sounds under different planes of anesthesia. It was observed that there was a definite shift of the intensity of the first and second sounds as one was anesthetized to stage III, plane 3 or 4. During the awakened state or during light anesthesia, the first sound was of higher pitch and greater intensity than the second. In moderate anesthesia the second sound was greater in intensity than the first, and in very deep anesthesia the intensity for both sounds was much lower and about equal.

More recently, Woodbridge (348) has published a paper dealing with a new division of what we call anesthesia into four separate categories. In Woodbridge's paper entitled "Changing Concepts Concerning Depth of Anesthesia" this alteration is divided into four separate elements of anesthesia: sensory afferent, motor efferent, reflexes and mental or sleep. The depression of these four components which we ordinarily call general anesthesia, he has called nothria because he believes the word nothria is a better one than anesthesia in that nothria itself is defined as mental and motor inactivity with insensibility. Since at the present time there are no papers dealing with the relative concentration of anesthetics and the depression of these various four elements mentioned by Woodbridge, we will spend most or practically all of the time in this chapter trying to develop and correlate the concentrations of the anesthetic, cyclopropane, in the inspired air and in the blood with the different stages and planes of anesthesia as first described by Guedel and those described by Possati and his associates (258), using the electroencephalogram to define the seven different levels of anesthesia or the change from the awakened state to that of respiratory arrest.

PRELIMINARY STUDIES ON ANIMALS

Several studies have been made relative to the concentration of cyclopropane in the air necessary for the different levels of anes-

thesia and respiratory arrest. All of the studies were made using some method of rebreathing in a closed system in which the carbon dioxide was removed by soda lime, and oxygen and cyclopropane were added as needed.

Lucas and Henderson (190) first reported that 10 to 12 per cent cyclopropane in oxygen was necessary for anesthesia in cats and that respiratory arrest was not produced in two cats with cyclopropane concentration of 27 per cent and 30 per cent and one dog with 31 per cent although the depth of respiration was markedly reduced.

Shackell and Blumenthal (299) reported an extensive study on five monkeys in which repeated anesthesias were done; these monkeys were anesthetized a total of 160 hours and were gradually brought to the stage of respiratory arrest twenty-eight times. The concentration for good surgical anesthesia was 17 to 18 per cent, whereas that necessary for respiratory arrest was 33.7 per cent when the oxygen concentration was 20 per cent, and 25.7 per cent cyclopropane when the oxygen concentration was 70 per cent. The effect of high oxygen on respiration in monkeys under cyclopropane is in agreement with data found by Marshall and Rosenfeld (199) who have shown that the inhalation of pure oxygen by animals with a depressed respiratory center may further reduce or even abolish respiratory activity. See page 163, Chapter 4, for further discussion of this topic.

Seevers, Meek, Rovenstine, and Stiles (297) made a more extensive study of the concentrations of cyclopropane necessary for the different levels of anesthesia and respiratory arrest in a series of nineteen dogs and found that surgical anesthesia was produced by 18 to 22 per cent and respiratory arrest by 39 per cent. A table from their report is presented in table 7.

STUDIES ON MAN

Waters and Schmidt (341) made the only detailed study relative to the concentration of cyclopropane necessary in the inspired air for the production of the different planes of anesthesia and re-

Another method of determining the depth of anesthesia that might be developed is that investigated by Rence, Cullen, and Hamilton (264) in which cathode ray tracings were made of the heart sounds under different planes of anesthesia. It was observed that there was a definite shift of the intensity of the first and second sounds as one was anesthetized to stage III, plane 3 or 4. During the awakened state or during light anesthesia, the first sound was of higher pitch and greater intensity than the second. In moderate anesthesia the second sound was greater in intensity than the first, and in very deep anesthesia the intensity for both sounds was much lower and about equal.

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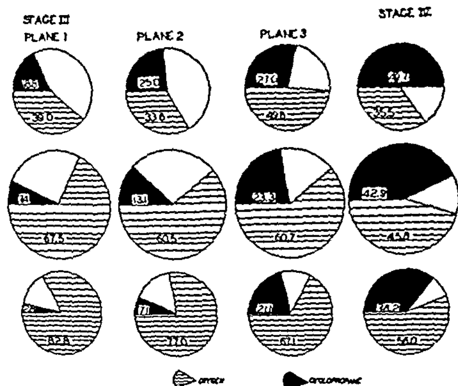


FIG. 5. Gas analyses of mask samples from forty-six cases taken during the various planes of surgical anesthesia and during the fourth stage (respiratory arrest) Upper circles show maximum concentration, lower circles show minimum, and large circles show the average percentage for each degree of narcosis. (Waters and Schmidt J. A M A , 103, 975, 1934).

too thoroughly worked out in man, but that of correlation with the various electroencephalographic levels has been worked out quite satisfactorily. In 1939, Smith (303) carried out some studies on the obstetrical patient in which he *determined the concentration of* cyclopropane in the maternal and fetal blood. He found in normal deliveries that the maternal circulation contained 12 mgm. per 100 cc. of arterial blood and 10.7 mgm. in the venous blood. Simultaneous fetal blood samples contained 9 6 mgm. per 100 cc. of arterial blood and 8 mgm. per 100 cc. of venous blood. In a later study, Rovenstine and his associates (287) reported the concentrations of cyclopropane in the blood necessary for spontaneous vaginal delivery, for forceps delivery, and for cesarean section.

TABLE 7*

Concentration of cyclopropane necessary for the different planes of anesthesia in the dog

Depth of Anesthesia (after Guedel)	No Premedication				Premedication			
	Number of analyses	Average cyclopropane concentration	Lowest concentration which would keep animal in given plane	Highest concentration of cyclopropane reached in this plane	Number of analyses	Average cyclopropane concentration	Lowest	Highest
		per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
III†—1‡ Corneal reflex − Wink reflex + Muscular relaxation ±	9	18.8	4 3	36.3	2	5.88	5.3	6.46
III—2 Wink reflex − Intercostal activity + Muscular relaxation +	20	24.7	9.7	46.9	3	12.75	7.57	20 3
III—3 and 4 Intercostal activity − Respiration very shallow	16	33.4	19.6	52.0	2	21.0	21.0	27.0
IV—Respiratory paralysis	8	39 4	21.0	56.8	1	31.0		
Concentration of cyclopropane reached without respiratory paralysis	7	44 0	35.0	58 8				

* Seevers *et al* J Pharmacol and Exper. Therap , 51, 1, 1934 (297).

† Roman, stage of anesthesia

‡ Arabic, plane of third stage.

spiratory arrest in surgical patients. Their patients had received morphine and scopolamine as preanesthetic medication. Their results are shown graphically in figure 5.

The correlation of the concentration of cyclopropane in the blood with the different planes of surgical anesthesia has not been

cyclopropane per 100 cc. of blood would be present at the time of the respiratory arrest in the human subject.

In 1953, Possati, Faulconer, Bickford, and Hunter (258) did a study on the electroencephalographic patterns during anesthesia with cyclopropane and correlated these changes with the concentrations of cyclopropane in the arterial blood. The studies of Possati and his associates were made upon fourteen human subjects, nine females and five males, who were undergoing major abdominal surgery with an average duration of anesthesia being 120 minutes. Their patients were premedicated as a rule with morphine 10 mgm. or methadone 10 mgm. plus the regular dose of atropine or hyoscine. An excerpt of their studies giving the characteristics of the different levels of anesthesia and the concentrations of cyclopropane present in these different levels is given in the following quotation:

> Classification of Levels.—A classification of electroencephalographic patterns occurring during cyclopropane anesthesia in man was made and it is described below. Typical patterns associated with each of the six levels described may be seen in figure 6. These levels represent progressively increasing depth of anesthesia
>
> First Level.—Dominating this level are high frequency waves of low amplitude ranging from 20 to 30 microvolts The alpha waves present in the preanesthetic period gradually disappear as the second level is approached. The first level usually lasts three or four minutes.
>
> Second Level—A sudden increase in amplitude marks the beginning of this level. The amplitude of the waves is in the range of 200 microvolts with a frequency of 4 to 8 cycles per second These waves have a regular form
>
> Third Level.—The pattern of this level is characterized by a complex tracing of mixed waves of high and low amplitudes. The range is from 50 to 200 microvolts Slow frequencies coexist with faster ones apparently at random.
>
> Fourth Level—In this level appears the first sign of suppression of cortical activity Small groups of waves with a frequency of 4 to 6 cycles per second and an amplitude of 40 to 60 microvolts are separated from the subsequent group of waves by an interval of relative suppression of cortical activity which does not last more than three seconds
>
> Fifth Level.—The period of suppressoin of cortical activity ranges from more than three seconds to not more than ten seconds and is alternated by the pres-

For vaginal delivery in six patients the concentration varied from 5 to 12 mgm. per 100 cc. with the fetal blood containing 12 mgm. per 100 cc. In twelve patients with forceps delivery the concentration of cyclopropane was 14 mgm. per 100 cc. and that in the fetus 13 mgm. per 100 cc. For eighteen patients with cesarean section the maternal blood contained 15 mgm. per 100 cc. and that in the fetus 10 mgm. per 100 cc. These values are moderately close to those found in the animal to produce moderate depths of surgical anesthesia.

Dripps (89), in his study on the immediate decrease in blood pressure seen at the conclusion of cyclopropane anesthesia, determined the concentration of cyclopropane in the blood during anesthesia in seven individuals. These concentrations varied from 5.5 mgm. to 20 mgm. per 100 cc. of blood with an average of 16 mgm. per 100 cc.

Stormont and his associates (314), in their study on the acid base balance in cyclopropane anesthesia in man, reported that during surgical anesthesia, stage III, planes 1 and 2, the concentration of cyclopropane varied from 10 to 21 mgm. per 100 cc. These patients, fifteen of them, had received morphine and scopolamine as preanesthetic medication.

Cohen and Beecher (62), in their study upon the effect of preanesthetic medication upon the concentration of cyclopropane in seventy-six patients, found an average of 13.6 mgm. per 100 cc. of blood (range 6 mgm. to 24 mgm.) at the time of full surgical anesthesia approximately one hour after the induction of anesthesia. As far as I have been able to find, no investigator has carried the patient to stage IV, respiratory arrest, and determined the concentration of cyclopropane in the blood although Waters has carried patients to respiratory arrest and determined the concentration of cyclopropane in the inspired air. If one could assume, and it is not too great an assumption, that the concentration of cyclopropane in the blood for respiratory arrest in man is similar or approximates that in the blood for respiratory arrest in the dog, then one might say that somewhere between 25 and 30 mgm. of

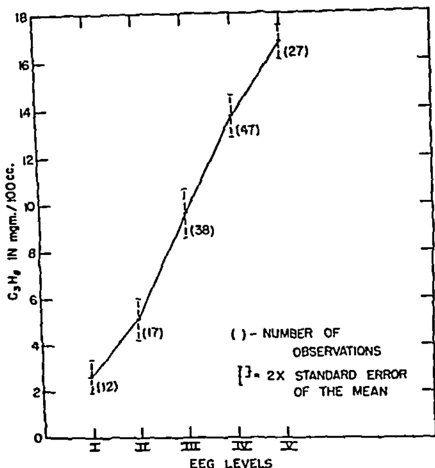


FIG 7 Correlation of electroencephalographic levels of surgical anesthesia in man with concentrations of cyclopropane in arterial blood. (After Possati *et al.*, Anesth & Analg, 32, 130, 1953).

analyzed for cyclopropane. Figure 7 shows in a graphic form the correlation between the means of the concentrations of cyclopropane in arterial blood and the electroencephalographic levels as assessed by the classification described, the number of observations, and twice the standard error of each mean. No data were available to correlate the arterial concentrations of cyclopropane with the sixth level.

It can be seen that the means of the concentrations of cyclopropane for each of the five levels designated reveal a remarkably high index of correlation with the electroencephalographic levels These means range from 2 62 mgm. of cyclopropane per 100 cc. of blood for the first electroencephalographic level to 16.9 mgm at the fifth level in what is almost a linear relationship on the graph

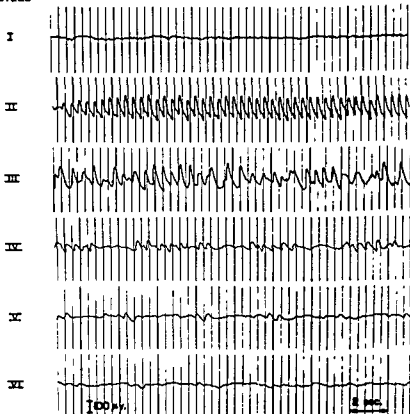


Fig 6 Classification of electroencephalographic patterns occurring during cyclopropane anesthesia These are arranged in order of increasing depth of anesthesia The third, fourth and fifth levels represent respectively light, moderate and deep surgical anesthesia A seventh level consisting of total inactivity probably exists but was not demonstrated in these studies. (After Possati *et al*: Anesth & Analg, 32, 130, 1953)

ence of small groups of waves with low amplitude and slow frequencies (2 to 3 per second and 20 to 40 microvolts)

Sixth Level —The dominant waves observed in the fourth and fifth levels disappear almost completely and the tracing appears as a flat line with some slight elevations and with an amplitude of 20 to 30 microvolts.

Correlation of Arterial Concentrations of Cyclopropane with Electroencephalographic Levels —One hundred forty-one arterial samples of blood were

The dogs were anesthetized by rebreathing into a bag containing a 30 to 40 per cent mixture of cyclopropane in oxygen. A Foregger metric machine was used to make up the gas mixture for the bag. After the dog was anesthetized deeply (usually required three to four minutes), the mask was removed and a tracheal catheter with an inflatable cuff inserted. The cuff was inflated to make an air-tight connection with the trachea. The catheter was then connected to a double valve which was in a closed circle with a soda lime filter and the Tissot spirometer containing the cyclopropane-oxygen mixture.

The concentration of cyclopropane in the spirometer was so adjusted at the beginning of the experiment that the animal was lightly anesthetized. The animal was kept on a fixed concentration of cyclopropane for fifteen to thirty minutes, at the end of which time tests were made for presence or absence of cornea reflex, abdominal relaxation, wink or lid reflex, and costal activity. The pulse and respiratory rates were recorded. The cyclopropane content of the expired air was determined two or three times during each experimental period and found to be constant, so we feel that equilibrium between the air and blood had been reached before the blood sample was drawn; an arterial blood sample was taken immediately after the last air sample for the quantitation of cyclopropane in the blood. Oxygen was continually admitted to the spirometer from a Foregger metric machine at the rate of oxygen consumption by the dog. Usually 100 to 200 cc. per minute were used.

The concentration of cyclopropane in the spirometer was increased by a few per cent each twenty or thirty minutes, so that we were able to ascertain nearly the exact air and blood cyclopropane concentrations at which the different reflexes were lost and respiratory failure occurred. From the blood and air-cyclopropane concentrations we were able to calculate the distribution ratio in vivo.

The cyclopropane concentration was always increased gradually until the respiration ceased, at which time the final blood sample was taken for analysis. In only one case out of twenty-one was it

TABLE 8*

Levels of surgical anesthesia

	Electroencephalographic Level	Blood-Cyclopropane Concentration
		mgm %
Control	0	0
Light.	II	5–10
Deep	III	10–15
Very deep	IV and V	15–21

* Li and Etsten: Anesthesiology, 18, 16, 1957 (186)

It should be pointed out, however, that a decided degree of variability existed in single observations of the concentration of cyclopropane in the blood at any one electroencephalographic level from patient to patient, especially in the third and fourth levels

In a study by Li and Etsten (186) upon the effect of cyclopropane anesthesia on cardiac output and related hemodynamics in man, careful correlation was made between the electroencephalographic levels and the concentration of cyclopropane in the blood at a given time. Their results are shown in table 8. Various subjects like those of Possati and his associates had received subcutaneous doses of morphine, 5.2 to 10 mgm. per patient plus scopolamine .3 to .4 mgm. per patient, before the anesthetic was started.

These data on the concentration of cyclopropane in the blood of man for the different planes of surgical anesthesia and for the different electroencephalographic levels compare quite closely to those to be described in the animal later in this chapter.

FURTHER ANIMAL EXPERIMENT

Soon after the publication of the papers by Seevers and his associates (297) and Waters and Schmidt (341) upon the concentrations of cyclopropane in the inspired air necessary for the different planes of surgical anesthesia and respiratory arrest, I became interested in determining the concentration of cylcopropane in the blood for the different planes of anesthesia and for respiratory arrest in the experimental animal (273, 274).

to ten blood samples were drawn from the different dogs. Records of two experiments are given in table 9.

In the experiments there was a regular order of loss of reflexes. The knee jerk, which is abolished in ether anesthesia at a much higher concentration than abdominal rigidity, is the first to disappear; the corneal reflex follows next with an 18 per cent mixture; the abdomen is well relaxed with a 22 per cent mixture; the lid or wink reflex is abolished at 27 per cent; and the costal muscles lose their activity at an average of 33 per cent. Respiratory arrest was produced at 36 per cent. These are average values for the seventeen dogs of which the more complete data are given in table 10.

The variation in the concentration of cyclopropane required to produce the same stage of anesthesia in the different dogs is much greater than similar variations with ether anesthesia. The distribution ratio in vivo, blood-cyclopropane concentration/air-cyclopropane concentration, varied from 0.421 to 0.596 with an average of 0.492, but in only three of the seventeen experiments did the values differ from the average by as much as 6 per cent. The average of 0.492 is very close to the values of 0.49 to 0.52 in vitro as recorded in figure 2 for the blood of dog and man.

The values for the concentration of cyclopropane in the air

TABLE 10*

Concentrations of cyclopropane in the air and blood required for loss of reflexes and respiratory arrest in dogs

Reflexes	Number of Animals	C_3H_6—Per Cent in Air			C_3H_6—Milligrams per 100 cc Blood			Average Distribution Ratio
		Average	Minimum	Maximum	Average	Minimum	Maximum	
Loss of corneal reflex	9	18 0	16 0	21.0	13 9	11.1	15.9	0.490
Abdominal relaxation	16	22.3	17 0	30.0	16.8	12.1	22.4	0.492
Loss of wink reflex	14	27 3	19 0	34 5	20 6	12.7	25.7	0.500
Costal paralysis	14	33 6	28.6	43 8	25 5	21.6	31.6	0.497
Respiratory arrest	10	35.8	30 0	44 5	28 2	22.4	33.8	0.492

* Robbins: J Pharmacol and Exper. Therap., 58, 251, 1936 (273).

impossible to reestablish respiration, and in this dog we were unable to give artificial respiration for three to four minutes after normal breathing ceased. With the other dogs the tracheal catheter was disconnected from the anesthetic circle within a minute after respiration ceased, and in most instances spontaneous breathing began after two or three compressions of the thorax and abdomen.

Twenty-one dogs were studied by this method. The duration of anesthesia varied from two and one-half to seven hours, and three

TABLE 9*

Experiment Number	Dog Weight	Time on Mixture	Per Cent C_3H_6 in Oxygen	Condition of Reflexes					Respiration Rate	Heart Rate	Concentration of C_3H_6		Distribution Ratio Blood Conc / Air Conc
				Knee jerk	Corneal reflex	Abdominal rigidity	Wink reflex	Costal activity			Arterial blood	Air	
	kgm	*min*									*mgm per 100 cc*	*mgm per 100 cc*	
6	6 5	Normal	0	+	+	+	+	+	28	140			
		20	15 4	−	+	+	+	+	36	120	11.6	23.7	0 490
		30	18.6	−	−	+	+	+	36	112	14.8	28 6	0 518
		40	24 6	−	−	−	+	+	30	120	19.4	37 9	0.512
		60	24 6	−	−	−	−	+	40	90	19.4	37 9	0.512
		30	32 0	−	−	−	−	−	32	120	24.4	49.2	0 496
		30	37 0	−	−	−	−	−	32	88	28.4	57 0	0 499
		50	37 0	Respiration ceased. Revived.							28.4		(Av. 0 505)
13	9 1	Normal	0	+	+	+	+	+					
		30	18 0	−	−	+	+	+	60	72	12.4	27.6	0.450
		30	21 2	−	−	+	+	+	60	90	15.9	32.6	0 488
		30	25 6	−	−	+	+	+	60	102	19.2	39.4	0.488
		30	30 6	−	−	−	+	+	96	102	22 4	47.0	0.477
		30	33 9	−	−	−	−	+	108	108	27 5	52.1	0 493
		30	38 6	−	−	−	−	+	120	96	27.0	59 5	0.455
		45	43 8	Respiration ceased Revived.							33 8	67.5	0.500 (Av. 0 480)

* Robbins: J Pharmacol and Exper Therap., 58, 251, 1936 (273).

morphine or methadone are more similar or better comparable to those in the dog that has received morphine 2 to 5 mgm. per kilo than in the dog that has had no premedication whatsoever. Greisheimer and her associates (117–121) have made numerous studies upon the effect of ether, pentothal, and morphine upon the concentration of cyclopropane necessary for the production of anesthesia. In her studies the dogs without premedication required an average of 18 to 19 mgm. of cyclopropane per 100 cc. of blood for the average plane of anesthesia in which she ran her experiments. In dogs that had preanesthetic medication, approximately half of the anesthetic dose of pentothal, the concentration of cyclopropane was 10.7 mgm. per 100 cc. In the dogs that had had morphine sulfate 3 mgm. per kilo, the concentration of cyclopropane was reduced from the average of 19.7 mgm. per 100 cc. to 9.9 mgm. per 100 cc. of blood. These values are quite close to those to be mentioned later as reported by Robbins.

The work of Calderone (57), who is one of the few that determined the concentration of ether in the blood necessary for surgical anesthesia and respiratory arrest after premedication in dogs, showed that morphine or subanesthetic doses of amytal did not reduce the amount of ether necessary for anesthesia or respiratory arrest. He stated in summary that the margin of safety in ether anesthesia is neither increased nor decreased by preliminary medication with sedative doses of morphine or the barbiturates that he used; the advantage of giving morphine or barbiturates lies in the mental and physical relaxation they produce.

A study at the University of Chicago by Livingstone and her associates (188), on the effect of morphine premedication upon the amount of ether in the blood of patients, failed to show that the amount of ether required for a given plane of stage III was any less than the amount in non-premedicated patients.

In the study by Cohen and Beecher (62) the concentration of cyclopropane in the control group was 13.6 mgm. for 100 cc., in the morphine group was 13.2 mgm. per 100 cc., and in the pentobarbital groups was 13.9 mgm. for 100 cc., so at least in man the

necessary for the different planes agree remarkably well with the values found by Seevers *et al.* as shown in table 7.

Fay, Andersch, and Kenyon (99), using the Orcutt-Seevers modification of the Van Slyke-Neill technic, found the concentration of cyclopropane in the blood during surgical anesthesia in five dogs to vary from 12.9 to 27 mgm. per 100 cc. with an average of 20 mgm.

Greisheimer and her associates (117–121) in many studies have found the concentration of cyclopropane in the blood for various stages or planes of anesthesia to extend over a range from 9.46 to 29 mgm. of cyclopropane per 100 cc. of blood with an average of 19.7 mgm. per 100 cc. These figures are in close agreement with those reported by Robbins.

EFFECT OF PREMEDICATION UPON THE CONCENTRATION OF CYCLOPROPANE NECESSARY FOR ANESTHESIA AND RESPIRATORY ARREST

In the report of Waters and Schmidt (341) the patients had received morphine and scopolamine as preanesthetic medication, and as a rule all surgical patients receive some type of preanesthetic medication to quiet them, and at times the dose given is of such magnitude that it is expected to reduce the amount of the anesthetic necessary for the desired level of anesthesia.

The relatively low concentrations of cyclopropane found by Waters and Schmidt in their patients during the lighter planes of stage III in contrast to the amount necessary in non-premedicated dogs for comparable levels are due in all probability in part to the premedication. Seevers *et al.* (297) found in four dogs premedicated with morphine that the concentrations of cyclopropane for anesthesia were reduced some 12 per cent without a corresponding reduction in the amount necessary for respiratory arrest; thus the premedication increased the margin of safety of cyclopropane.

The values given for the concentrations of cyclopropane in the blood found by Possati and his associates (258) and Li and Etsten (186) in patients who had preanesthetic medication with either

TABLE 11*

Effect of premedication upon the concentration of cyclopropane necessary for anesthesia and respiratory arrest

Number of Experiments	Premedication		C_3H_6 Mgm per 100 cc Blood for			
	Type	Mgm per kgm	Abdominal relaxation	Loss of wink reflex	Intercostal paralysis	Respiratory arrest
17	Control		16.8	20 6	25.5	28.2
3	Morphine	2	8.7	15.1	24	29.9
5	Morphine	5	6 0	12.4	21.1	28.3
4	Morphine	10	5 0	6.7	16.9	20.3
4	Barbital sodium	150	5.6	10.4	18.7	24.1
4	Barbital sodium	250	3.9	7.1	12 5	16.4
4	Amytal sodium	30	6.9	11.9	22.0	29.3
4	Amytal sodium	45	5	6.9	17.1	25.2

* Robbins, Baxter, and Fitzhugh: J. Pharmacol. and Exper. Therap., 65, 136, 1939 (278).

in dogs, which Calderone states is equivalent to a 10 mgm. dose in man, the blood concentration of cyclopropane required to produce abdominal relaxation is reduced 48 per cent, that required for abolition of the wink reflex is reduced 27 per cent, whereas the amount required for respiratory arrest is not reduced at all. This factor increases the margin of safety with cyclopropane very definitely. A dose of morphine of 5 mgm. per kilogram in the dog, which Calderone states is equal to a 25 mgm. dose in man, reduced the amount of cyclopropane for surgical anesthesia 40 to 64 per cent but did not alter the concentration required for respiratory arrest. Demerol, 10 mgm. per kilogram, reduced the amount of cyclopropane in the same order as that of 2 and 5 mgm. of morphine.

The effects of morphine in 8 and 10 mgm. per kilogram doses are noted in all stages and at respiratory arrest.

Barbital sodium, in 150 mgm. per kilogram dose, which is about one-half the anesthetic amount, reduced the cyclopropane required for surgical anesthesia 11 mgm. per 100 cc., or about 65 per cent, whereas the amount required for respiratory arrest is reduced only 4 mgm per 100 cc., or 15 per cent.

preanesthetic administration of morphine or pentobarbital does not reduce the amount of cyclopropane necessary for surgical anesthesia according to their results.

The effects of small doses of pentothal upon the quantity of cyclopropane necessary for anesthesia have been most clearly shown with the least possible human observer element involved by Bellville and Artusio (17). In this study, the regulation of the flow of cyclopropane was under the subject's own electroencephalographic pattern through the servo mechanism. After the subject had been running along for quite some time, small amounts of pentothal, 25 to 50 mgm., were given intravenously to human subjects in a fixed level of cyclopropane anesthesia. This small dose of pentothal altered the electroencephalographic pattern to such an extent that the servo mechanism immediately reduced the flow of cyclopropane to the patient. This must be an example of summation of the effects of pentothal and cyclopropane.

We (278) have reported studies in which the concentrations of cyclopropane necessary in the blood for the different levels of anesthesia and respiratory arrest were determined in thirty-eight dogs after medication with morphine, demerol, barbital, or amytal. Morphine was given subcutaneously, 2 to 10 mgm. per kilogram; demerol was given subcutaneously in a dose of 10 mgm. per kilogram, barbital sodium was given intravenously, 150 to 250 mgm. per kilogram (50 to 85 per cent of the anesthetic dose); amytal sodium was given intravenously, 30 to 45 mgm. per kilogram (50 to 75 per cent of the anesthetic dose). Thirty minutes after premedication the dogs were anesthetized as described on page 22. Blood samples were collected at the different planes of anesthesia and the cyclopropane content determined. The average values are shown in table 11.

Although the number of animals used in this study is limited, it is evident that the amount of cyclopropane necessary for the production of the lighter planes of stage III anesthesia is very markedly diminished after premedication with morphine, demerol, barbital, or amytal. With morphine in 2 mgm. per kilogram dose

studies except that 10 cc. samples of blood were taken from the right ventricle one-half to one minute after the samples from the artery. At the end of each experiment an autopsy was performed and the heart carefully examined for needle punctures in the left ventricle and auricle. In no instance were any punctures found, so we feel certain that we were collecting venous blood from the right side of the heart. After the animal had been on a fixed concentration for fifteen minutes or longer, the cyclopropane content of the venous blood was approximately equal to that of the arterial blood. The results of these studies are shown in table 12.

TABLE 12*

Cyclopropane concentrations of arterial and mixed venous blood in relation to cyclopropane content of air

Dog Number	Sample	Cyclopropane		
		Air corrected	Arterial blood	Venous blood
		mgm per 100 cc	*mgm per 100 cc*	*mgm per 100 cc.*
18	1	32.8	17.3	16.8
	2	37.4	20.5	20.7
	3	45.4	22.4	20.0
	4	49 5	21 3	21.0
	5	47 8	24.6	24 3
	6	60 3	28.9	27.8
19	1	30.8	15.4	15.1
	2	28 8	14 0	13.5
	3	41.8	20.5	20.8
	4	48 8	27 2	25 9
	5	55 8	31 3	31 8
20	1	30 8	13 5	14.6
	2	37 0	17.5	17 3
	3	47 0	22.2	21 4
	4	53 1	27.0	26.8
	5	41 4	18.9	18 1
	6	22.2	11.6	11 0

* Robbins: J. Pharmacol and Exper. Therap , 58, 251, 1936 (273)

Barbital sodium, in 250 mgm. per kilogram dose, replaced 11 to 13 mgm. of cyclopropane in all levels of anesthesia.

Amytal, in 30 mgm. per kilogram dose, causes changes in the cyclopropane concentrations required for the different levels of the same order as 5 mgm. doses of morphine.

Amytal, in 45 mgm. per kilogram dose, produced effects parallel to those of 150 mgm. doses of barbital sodium.

TIME REQUIRED FOR EQUILIBRIUM OR SATURATION TO BE ATTAINED WITH CYCLOPROPANE

In several reports from clinical anesthetists (96, 223) it is stated that after the patient is in the desired plane of anesthesia, the flow of cyclopropane into the bag can be cut to a very low rate or stopped completely for several minutes. This would indicate that equilibrium is reached relatively rapidly and that cyclopropane is not destroyed in the body to any extent.

The rate of saturation or desaturation with a gas is dependent mainly on three factors: its solubility in blood, tissue, and fat; the rate of circulation (cardiac output); and the respiratory minute volume. With cyclopropane, which has a distribution ratio between air and blood of .45 to .5 as compared to 14 for ether, the cardiac output or circulation rate would play the major role in the rate of saturation.

We have made a study in which the concentration of cyclopropane in the anesthetic mixture was correlated with the concentration in the arterial and mixed venous blood in an attempt to determine the approximate rate of saturation, the procedure and results of which are given below.

RELATION OF CYCLOPROPANE CONTENT OF AIR, ARTERIAL AND MIXED VENOUS BLOOD IN DOGS

In three dogs the cyclopropane content in blood taken from the right ventricle was compared with that from the femoral artery and inspired air. The procedure was the same as for the preceding

studies except that 10 cc. samples of blood were taken from the right ventricle one-half to one minute after the samples from the artery. At the end of each experiment an autopsy was performed and the heart carefully examined for needle punctures in the left ventricle and auricle. In no instance were any punctures found, so we feel certain that we were collecting venous blood from the right side of the heart. After the animal had been on a fixed concentration for fifteen minutes or longer, the cyclopropane content of the venous blood was approximately equal to that of the arterial blood. The results of these studies are shown in table 12.

TABLE 12*

Cyclopropane concentrations of arterial and mixed venous blood in relation to cyclopropane content of air

Dog Number	Sample	Cyclopropane		
		Air corrected	Arterial blood	Venous blood
		mgm per 100 cc	*mgm per 100 cc*	*mgm per 100 cc.*
18	1	32 8	17 3	16 8
	2	37.4	20.5	20.7
	3	45.4	22.4	20.0
	4	49 5	21.3	21 0
	5	47.8	24.6	24 3
	6	60.3	28.9	27 8
19	1	30 8	15 4	15.1
	2	28 8	14 0	13 5
	3	41.8	20 5	20 8
	4	48.8	27.2	25.9
	5	55.8	31 3	31.8
20	1	30.8	13.5	14 6
	2	37.0	17.5	17 3
	3	47.0	22 2	21.4
	4	53 1	27 0	26.8
	5	41 4	18.9	18.1
	6	22 2	11 6	11 0

* Robbins J Pharmacol. and Exper. Therap., 58, 251, 1936 (273)

RATE OF ELIMINATION OF CYCLOPROPANE AFTER ITS ADMINISTRATION IS STOPPED

Dogs

For this study the dog was anesthetized for two to three hours so that the tissues would have a relatively high cyclopropane content. The concentration of cyclopropane in the inspired mixture was maintained at 25 to 30 per cent. The blood samples were taken from the right auricular by means of a catheter which was passed through the right external jugular vein to the auricle. At fifteen minutes, and again at one minute, before the administration of the anesthetic was discontinued, blood samples were drawn for analysis. At regular intervals during the first two hours after the anesthetic was stopped, blood samples were taken and their cyclopropane content determined. The elimination of cyclopro-

TABLE 13*

Rate of elimination of cyclopropane

Time	Condition of Dog	Milligrams C_3H_6 per 100 cc. Venous Blood		
		Dog 1	Dog 2	Dog 3
a m				
10:00	Deep anesthesia	20 5	20 3	20.0
10:14	Deep anesthesia	23.7	22.3	18.5
10:15	Administration of C_3H_6 stopped			
10:17 5	Moving head	6 3	7.1	10.0
10:20	Awake	4 7	4.7	7.9
10:25	Awake	2 6	4.4	4.7
10:30	Awake	1.6	2 6	2.9
10:45	Awake	0 8	1.6	2.1
11:00	Awake	†	†	1.6
11:15	Awake	0 8	1 3	1.3
11:45	Awake	†	1 0	1.0
12:15	Awake	0	0 8	0 5

* Robbins J Pharmacol and Exper Therap, 58, 251, 1936 (273)

† No samples taken at these points

pane is much more rapid than the elimination of ether reported by Ronzoni (284). This difference in rate of elimination of cyclopropane and ether may be accounted for by the difference in the distribution ratios of these agents between air and blood mixtures. The results of three such experiments are given in table 13 and figure 8.

Mice

The mouse was weighed and placed in a 20-liter bottle containing cyclopropane in air; a bag of soda lime was added to take up the carbon dioxide. After 30 minutes the concentration of cyclopropane in the air was determined, the mouse was removed and

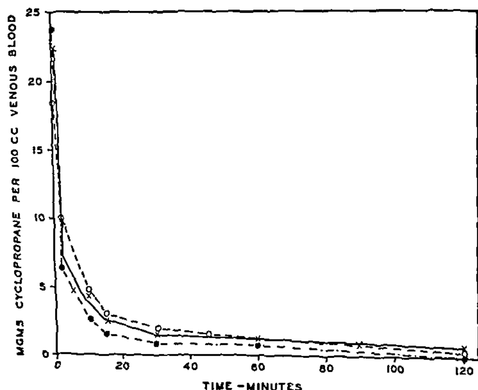


FIG 8 Elimination of cyclopropane in dogs after two to three hours of deep anesthesia Blood samples were taken from the right auricle immediately before and at regular intervals after the administration of cyclopropane was stopped (Robbins Anesth. & Analg., 16, 93, 1937)

RATE OF ELIMINATION OF CYCLOPROPANE AFTER ITS ADMINISTRATION IS STOPPED

Dogs

For this study the dog was anesthetized for two to three hours so that the tissues would have a relatively high cyclopropane content. The concentration of cyclopropane in the inspired mixture was maintained at 25 to 30 per cent. The blood samples were taken from the right auricular by means of a catheter which was passed through the right external jugular vein to the auricle. At fifteen minutes, and again at one minute, before the administration of the anesthetic was discontinued, blood samples were drawn for analysis. At regular intervals during the first two hours after the anesthetic was stopped, blood samples were taken and their cyclopropane content determined. The elimination of cyclopro-

TABLE 13*

Rate of elimination of cyclopropane

Time	Condition of Dog	Milligrams C_3H_6 per 100 cc Venous Blood		
		Dog 1	Dog 2	Dog 3
a m				
10:00	Deep anesthesia	20.5	20 3	20 0
10:14	Deep anesthesia	23 7	22.3	18.5
10.15	Administration of C_3H_6 stopped			
10:17.5	Moving head	6 3	7.1	10 0
10:20	Awake	4 7	4 7	7.9
10:25	Awake	2.6	4 4	4.7
10:30	Awake	1 6	2 6	2.9
10:45	Awake	0.8	1.6	2 1
11:00	Awake	†	†	1.6
11:15	Awake	0 8	1.3	1 3
11:45	Awake	†	1 0	1.0
12.15	Awake	0	0 8	0.5

* Robbins· J Pharmacol and Exper Therap., 58, 251, 1936 (273).

† No samples taken at these points.

propane in mixed venous blood after anesthesia is stopped, and (d) the rapid excretion of cyclopropane from mice after 30-minute anesthesia, saturation and desaturation of the tissues occur at a very rapid rate.

SUMMARY

There is close agreement between the concentrations of cyclopropane necessary for the different levels of anesthesia and respiratory arrest in man, monkey, dog, and cat.

The concentration of cyclopropane in the blood is proportional to that in the alveoli after the dog has been on a fixed concentration for 15 to 30 minutes, at which time the amount in the mixed venous blood is equal to that in the arterial blood.

Premedication with morphine, barbital, or amytal definitely reduced the amount of cyclopropane for anesthesia without a comparable reduction in the amount necessary for respiratory arrest. This would indicate that premedication increases the margin of safety of cyclopropane in the dog.

The concentrations of cyclopropane in the blood of the human subject for the different planes of surgical anesthesia or comparable EEG levels are quite similar to those observed in the dog that has had premedication with morphine, demerol, or barbiturates.

With cyclopropane as with other general anesthetic agents, it requires about three-fifths as much drug to produce moderate anesthesia as it does to produce respiratory arrest.

placed immediately in a 700 cc. flask which was attached to the I_2O_5 oxidation train; air was drawn through the tube at the rate of 500 cc. per minute, and the I_2 liberated by the oxidation of cyclopropane, as it was exhaled, was collected in the KI tubes; fresh tubes were placed in line each 10-minute period for one hour. Five mice were used in this type of experiment. The average final concentration in the 20-liter bottle at the end of the 30-minute periods was 16.5 per cent.

Table 14 gives the results obtained in these experiments, recorded as mgm. cyclopropane per 100 grams mouse, recovered each 10-minute period. In an experiment in which the collection of cyclopropane was continued for two hours, only 3.8 per cent as much was recovered during the second as during the first hour.

We feel then that (a) in the light of clinical reports, (b) the fact that the cyclopropane content in the mixed venous blood is approximately equal to that in the arterial which is in equilibrium with that in the anesthetic mixture in the alveoli after fifteen minutes on a fixed concentration, (c) the rapid diminution of cyclo-

TABLE 14

Elimination of cyclopropane by mice

Experiment Number	Mgm C_3H_6 Recovered per 100 gram Weight 10 minute Intervals						Total
	0–10	11–20	21–30	31–40	41–50	51–60	
1	15 8	6.2	3 9	2 2	9	.3	29 3
2	20 5	10.2	4 4	1.9	1 3	6	38.9
3	20	5.0	5 4	1.2	1.2	1 3	34 1
4	19 6	8.9	3 9	2 4	1.2	.6	36.6
5	17 5	4 9	2 3	1	.6	.4	26.7
Average	18 7	7 04	3 98	1.74	1 04	604	33 1
Per cent of total per 10-min interval	56 4	21 2	11 8	5 7	3 1	1 8	
Per cent of total additive	56 4	77 6	89.4	95 1	98 2	100	

propane in mixed venous blood after anesthesia is stopped, and (d) the rapid excretion of cyclopropane from mice after 30-minute anesthesia, saturation and desaturation of the tissues occur at a very rapid rate.

SUMMARY

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The concentration of cyclopropane in the blood is proportional to that in the alveoli after the dog has been on a fixed concentration for 15 to 30 minutes, at which time the amount in the mixed venous blood is equal to that in the arterial blood.

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The concentrations of cyclopropane in the blood of the human subject for the different planes of surgical anesthesia or comparable EEG levels are quite similar to those observed in the dog that has had premedication with morphine, demerol, or barbiturates.

With cyclopropane as with other general anesthetic agents, it requires about three-fifths as much drug to produce moderate anesthesia as it does to produce respiratory arrest.

3

The Effects of Cyclopropane Anesthesia upon the Circulatory System

In the first papers by Lucas and Henderson (146, 147, 190) on cyclopropane anesthesia it was reported that temporary irregularities were observed on the blood pressure record of the cat, which they suggested were due to dropped beats. They observed that these irregularities were more apt to develop with a sudden change in concentration of cyclopropane or when the concentration was high; lowering the concentration by adding oxygen promptly abolished these abnormalities of rhythm. They reported that the blood pressure was not changed until the stage of respiratory arrest was approached.

Before Waters and his associates began their studies of cyclopropane on man, Seevers, Meek, Rovenstine, and Stiles (297) made a comprehensive study of cyclopropane upon dogs, correlating the concentration of cyclopropane in the alveoli with the planes of anesthesia, respiratory rate and volume, and cardiac rhythm by means of electrocardiographic records. A paragraph from their paper is quoted below:

> Cardiac arrhythmias occur with high concentrations of cyclopropane. The concentration required to initiate these irregularities is in the same range as that required to produce respiratory paralysis, which usually occurs a few minutes prior to or following arrhythmia These arrhythmias usually disappear as artificial respiration is instituted or the concentration lowered by adding oxygen. This agent, like ether, is sufficiently toxic to produce cardiac paralysis even under artificial respiration in the presence of an adequate alveolar tension of oxygen These concentrations are, however, far above the anesthetic range (above 60 per cent). The initial irregularities seen are probably of vagal origin since they are abolished by atropine. It is quite evident that these arrhythmias are not indicative of permanent cardiac change since a normal rhythm invari-

ably returns and remains regular as the concentration is diminished by adding oxygen.

The types of irregularities they observed at the time or soon after respiratory arrest were nodal beats, nodal extrasystoles, nodal rhythm, auriculoventricular block, idioventricular rhythm, ventricular extrasystoles, ventricular tachycardia, and auricular flutter.

Since cardiac irregularities of these types had been reported to occur in animals and man (4, 116, 185, 203) when anoxia was rapidly produced, and since Seevers *et al.* were able to abolish the irregularities by giving artificial respiration or decreasing the cyclopropane content by adding oxygen, we were of the opinion that the irregularities they observed at the time of or soon after respiratory arrest were due to anoxia and not to cyclopropane.

RELATION OF ARTERIAL OXYGEN CONTENT TO THE CARDIAC IRREGULARITIES AT THE TIME OF RESPIRATORY ARREST IN DOGS

Robbins and Baxter (275) have repeated the work of Seevers *et al.* but made analyses of the blood for oxygen, carbon dioxide, and cyclopropane, in addition to electrocardiographic studies. Their work is reported below.

Methods Used

Electrocardiographic study. A standard Cambridge electrocardiograph was used The records were taken from lead II and analyzed for rate, P-R interval, and T-wave changes, as well as for abnormalities.

Blood gases. The Van Slyke-Neill (253) manometric apparatus was used for the oxygen and carbon dioxide analyses. Arterial blood was collected under oil and 1 cc. samples were analyzed; duplicate analyses were not made as a routine. Control samples were taken immediately before the anesthesia was started. The presence of cyclopropane in the later blood samples does not inter-

fere with the oxygen and carbon dioxide determinations, as shown by Orcutt and Waters (240).

The cyclopropane content of the blood was determined on 5 cc. samples by the iodine-pentoxide oxidation method as described above.

Artificial respiration. A small respirator, a modification of the Drinker-Collins machine, was used after the animals' own respiratory activity had ceased. The rate as well as the amplitude of inspiration and expiration could be changed at will, but usually a rate of 21 per minute with an inspiratory pressure of −10 mm. of mercury and an expiratory pressure of 6 mm. was used.

Preparation of anesthetic mixture and mode of administration. A Foregger metric machine was used to supply the cyclopropane and oxygen. A soda lime cannister was used in a to-and-fro line to absorb the carbon dioxide. The dogs were anesthetized by rebreathing into a 6-liter bag containing a 30 to 40 per cent mixture of cyclopropane in oxygen. After anesthesia was sufficiently deep to permit it, a tracheal catheter with an inflatable cuff was inserted and then connected in line with the filter and bag. The bag was emptied and refilled two or three times during the experiment in order to remove the inert gas. Oxygen was added continuously at the rate of its consumption.

Animal Experiments on Dogs

The dog was attached on its back to the dog board and connections made for taking electrocardiographic records. A control record was taken. The right femoral artery was exposed under procaine anesthesia and a control arterial sample taken. Anesthesia was induced as stated above, after which the cyclopropane concentration was so adjusted as to maintain the animal at a fixed level of anesthesia for 30 minutes. The image of the electrocardiograph string was under constant observation, and records were taken during the induction and at definite intervals thereafter. Records were also taken of any irregularities noted. After 30 and 60 minutes of anesthesia, arterial samples were taken for analysis.

Electrocardiographic records were made at the time of blood sampling. After 60 minutes' anesthesia, the concentration of cyclopropane was increased gradually until respiration stopped, at which time an arterial sample was collected.

Blood gases, cyclopropane, and electrocardiographic studies in the normal dog. In the first group of experiments the dogs were anesthetized as above and arterial samples taken for oxygen and carbon dioxide analysis, as well as for cyclopropane. Except for the first two dogs (5A and 6A, table 15), we waited until cardiac irregularities developed after respiratory arrest before starting the respirator. An arterial sample was taken for oxygen and carbon dioxide analysis as soon as irregularities were shown by the image of the string of the electrocardiograph.

After irregularities developed, the respirator was started and the concentration of cyclopropane in the inspired air was further increased; arterial samples were taken at 15 to 30-minute intervals during the rest of the experiment, and a final sample taken when irregularities developed the second time.

The results of these experiments are given in table 15, in which are recorded the control oxygen, carbon dioxide, and heart rate; the oxygen, carbon dioxide, cyclopropane, and heart rate in deep surgical anesthesia; the oxygen, carbon dioxide, cyclopropane, and heart rate at time of respiratory arrest; and the oxygen and carbon dioxide present at the onset of cardiac irregularities. In that part of table 15 headed "Artificial Respiration", the arterial oxygen, carbon dioxide and cyclopropane concentrations, and heart rate, at the time of the highest cyclopropane content with electrocardiographic records still normal, are recorded in the first column; similar data are recorded for the blood gases at time of onset of the terminal irregularities. The final column records the duration of the experiment. In three of these nine experiments it was impossible to re-establish normal cardiac function after irregularities developed, but in these the onset of irregularities was 4, 12, and 10 minutes after respiration ceased.

In the central column headed "Cardiac Arrhythmia" the ar-

TABLE 15*

The concentration of carbon dioxide, oxygen, and cyclopropane in arterial blood in relation to the cardiac irregularities which develop at the time of or soon after respiratory arrest produced by cyclopropane

Experiment Number	Normal Respiratory Activity: Awake: Arterial CO_2	Awake: Arterial O_2	Awake: heart rate	Surgical anesthesia III_{3-4}†: Arterial CO_2	Surgical: Arterial O_2	Surgical: Arterial C_3H_6	Surgical: Heart Rate	Respiratory arrest IV: Arterial CO_2	Resp. arrest: Arterial O_2	Resp. arrest: Arterial C_3H_6	Resp. arrest: Heart rate	Cardiac Arrhythmia: Arterial CO_2	Cardiac Arrhythmia: Arterial O_2	Onset after respiratory arrest	Type‡	Artificial Respiration—Drinker Collins: Normal E K G: Arterial CO_2	Normal E K G: Arterial O_2	Normal E K G: Arterial C_3H_6	Normal E K G: Heart rate	Abnormal E K G: Arterial CO_2	Abnormal E K G: Arterial O_2	Abnormal E K G: Arterial C_3H_6	Abnormal E K G: Type	Duration of Anesthesia to Respiratory Arrest / Total Duration of the Experiment
	per cent	per cent		per cent	per cent	mgm		per cent	per cent	mgm		per cent	per cent	min		per cent	per cent	mgm		per cent	per cent	mgm		
5A	39.3	22.6	135	38.8	23.1	25.0	150	57.0	8.3	34.5	165					37.6	13.9	43.5	150	42.5	2.5	43.0		82/160
6A	45.3	14.4	85	45.7	19.4	17.7	220	54.5	11.0	28.5	200					37.5	14.6	44.5	130	29.0	5.5			60/160
7	34.6	15.1	150	38.3	15.6	24.4	180	51.0	7.1	32.8	100	49.5	1.3	3.0	V. Ex	28.8	15.0	39.0	110	29.4	11.5	40.0	V. Ex.	83/136
8	41.8	17.3	115	45.7	20.4	28.5	170	53.0	19.9	33.8	130	62.2	2.4	5.5	Arrest, N. R.	30.5	18.2	46.7	150	30.0	18.4	44.2	V. Ex.	50/100
9	40.8	19.5	100	43.1	20.8	28.0	240	50.6	19.2	34.6	150	59.0	2.1	8.0	Block; Arrest	26.6	17.0	44.7	110	28.0	14.4	45.7	V. Fib	60/130
10	40.0	20.9	80	39.8	25.0	32.3	190	45.0	26.0	38.5	180	57.0	6.7	7.0	N. R	33.0	6.2	43.0	130	12.0	18.0	51.6	V. Fib	115/175
11	39.0	20.6	120	47.2	23.1	30.8	100	55.0	19.8	29.0	70	55.8	1.4	12.0	Arrest									52/61
13	40.4	19.9	110	45.1	17.9	28.0	110	53.8	14.6	38.5	70	59.0	0.48	10.0	N. R									54/61
14	43.0	13.8	150			24.2	170	49.0	11.2	27.4	160	54.0	1.5	4.0	Arrest									30/31
Ave	40.5	18.2	126	42.7	20.6	26.5	170	52.1	15.2	33.0	146	56.5	2.27	7.1		32.3	14.1	43.6	130	29.2	12.2	43.3		
The vagi were cut after anesthesia was induced but before samples were taken for III_{3-4} in the following experiments 15–18																								
15	42.2	13.7	110	42.7	16.3	25.8	170	53.0	15.2	35.0	240	58.0	6.7	6.0	Arrest									124/130
16			110	38.7	19.2	30.8	130	54.7	17.5	32.8	160					26.4	16.6	39.2	130	25.0	15.4	38.5	V. Fib.	90/180
17	42.5	19.5	105	48.2	19.3	26.2	160	60.0	11.3	34.2	160	63.0	0.9	2.0	N. R V Ex	35.8	16.4	44.0	140	32.0	10.6	50.7	N. R.	118/232
18	39.4	22.4	110	37.0	23.0	27.0	160	46.0	19.1	38.5	190	57.0	4.8	3.0	N R. V. Ex	18.4	12.4	53.0	150	15.4	4.8	54.6	V Ex	105/225
Ave	41.4	18.5	109	41.7	19.5	27.4	155	53.4	15.8	35.1	187	59.3	4.1	3.7		26.2	15.1	45.4	140	24.1	10.2	47.9		

* Robbins and Baxter J Pharmacol and Exper Therap, 61 : 162, 1937 (275)

† Classification of depth of anesthesia after Guedel

‡ V. Ex = ventricular extrasystoles, Arrest = ventricular arrest, N R = nodal rhythm, Block = auriculoventricular block; V Fib. = ventricular fibrillation.

Electrocardiographic records were made at the time of blood sampling. After 60 minutes' anesthesia, the concentration of cyclopropane was increased gradually until respiration stopped, at which time an arterial sample was collected.

Blood gases, cyclopropane, and electrocardiographic studies in the normal dog. In the first group of experiments the dogs were anesthetized as above and arterial samples taken for oxygen and carbon dioxide analysis, as well as for cyclopropane. Except for the first two dogs (5A and 6A, table 15), we waited until cardiac irregularities developed after respiratory arrest before starting the respirator. An arterial sample was taken for oxygen and carbon dioxide analysis as soon as irregularities were shown by the image of the string of the electrocardiograph.

After irregularities developed, the respirator was started and the concentration of cyclopropane in the inspired air was further increased, arterial samples were taken at 15 to 30-minute intervals during the rest of the experiment, and a final sample taken when irregularities developed the second time.

The results of these experiments are given in table 15, in which are recorded the control oxygen, carbon dioxide, and heart rate; the *oxygen, carbon dioxide, cyclopropane, and heart rate in deep* surgical anesthesia, the oxygen, carbon dioxide, cyclopropane, and heart rate at time of respiratory arrest; and the oxygen and carbon dioxide present at the onset of cardiac irregularities. In that part of table 15 headed "Artificial Respiration", the arterial oxygen, carbon dioxide and cyclopropane concentrations, and heart rate, at the time of the highest cyclopropane content with electrocardiographic records still normal, are recorded in the first column; similar data are recorded for the blood gases at time of onset of the terminal irregularities. The final column records the duration of the experiment. In three of these nine experiments it was impossible to re-establish normal cardiac function after irregularities developed, but in these the onset of irregularities was 4, 12, and 10 minutes after respiration ceased.

In the central column headed "Cardiac Arrhythmia" the ar-

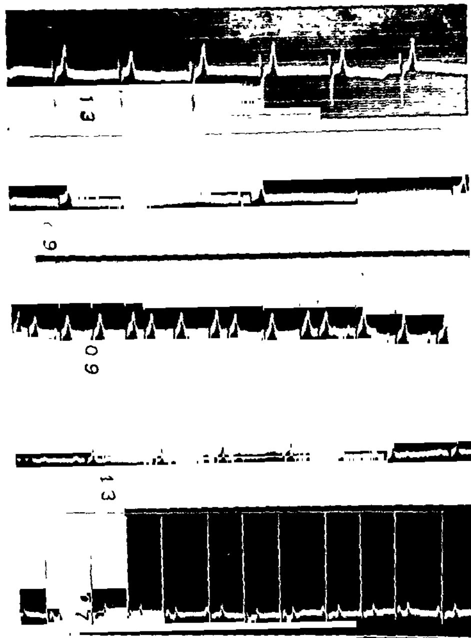


FIG 9 Electrocardiographic records from five dogs which received no preanesthetic medication The dogs were forced to respiratory arrest by gradually increasing the cyclopropane content of the anesthetic mixture. There were no cardiac irregularities present before respiratory arrest The irregularities shown above developed 4 3 minutes after respiratory arrest and with an arterial oxygen concentration of 3 9 volumes per cent. 13—ventricular extrasystole arising from a single focus 09—complete auriculoventricular dissociation with slow rates, auricles 32/1' [illegible]
AV block 2.1 [illegible]
ventricles irr[illegible]
(Robbins, Ba[illegible]

terial oxygen and carbon dioxide concentrations at time of onset and type of irregularities present are recorded. Figure 9 shows the first irregularities observed after respiratory arrest in 5 dogs. See table 15 and figure 9.

The concentration of cyclopropane in the arterial blood at the time of respiratory arrest in this series was 33 mgm. per 100 cc., *which is 17 per cent higher than similar data reported above* (Chapter 2); this difference is due to the variation in duration of anesthesia before respiratory arrest developed. In the earlier studies, the anesthesia was gradually deepened over periods of 2.5 to 7 hours to respiratory arrest, whereas in this series the average duration of the anesthesia was 1.1 hours before respiration stopped.

After the dogs were placed in the respirator, an average arterial cyclopropane concentration of 43.6 mgm. per 100 cc. of blood was reached before the heart became irregular; this is an increase of 31 per cent over the concentration required for respiratory arrest

The complete data of a typical experiment (no. 9) are given in table 16 with selected electrocardiographic records shown in figure 10. The arterial oxygen and carbon dioxide are both higher under deep anesthesia than in the normal. Similar findings in man under cyclopropane anesthesia were noted by Hathaway and Orcutt as quoted by Waters (339).

Blood gases, cyclopropane, and electrocardiographic studies in dogs with the vagi cut. In four dogs studied in the same manner as the group above, the vagi were sectioned after the animals were anesthetized. The data from these experiments are given in the lower section of table 15. From a comparison of the average values for the nine normal dogs with those of the four with vagi cut, one can say that the vagus has very little effect upon the arterial concentrations of oxygen, carbon dioxide, and cyclopropane at which respiration ceases and cardiac irregularities develop.

In table 17 the complete data are recorded from an experiment (no. 17) similar to that in table 16 except that in this dog the vagi

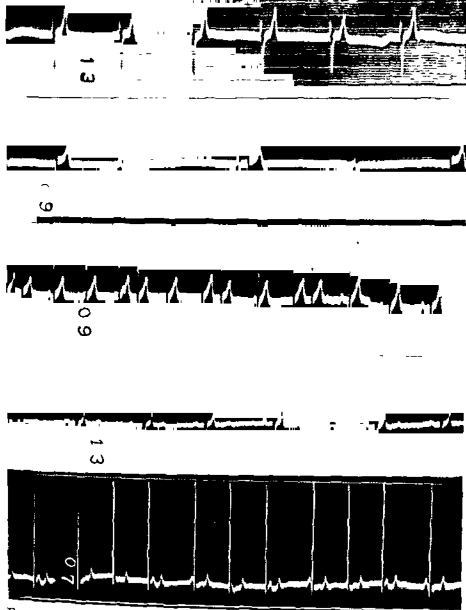


FIG 9 Electrocardiographic records from five dogs which received no preanesthetic medication: The dogs were forced to respiratory arrest by gradually increasing the cyclopropane content of the anesthetic mixture There were no cardiac irregularities present before respiratory arrest The irregularities shown above developed 4 3 minutes after respiratory arrest and with an arterial oxygen concentration of 3 9 volumes per cent 13—ventricular extrasystole arising from a single focus. 09—complete auriculoventricular dissociation with slow rates, auricles 32/1′, ventricles 20/1′. 09—tachycardia of nodal origin, 140/1′ 13—partial AV block 2:1 to 3:1 07—auriculoventricular dissociation—auricles regular, 100/1′, ventricles irregular, 100/1′. The shadow of the upstroke of R has been intensified (Robbins, Baxter, and Fitzhugh: Ann Surg , 110, 85, 1939)

TABLE 16*

Experiment 9. Normal dog

Time	Stage†	Arterial			E K G Number	Rate	P-R Interval	T Wave‡	Rhythm
		CO_2	O_2	C_2H_4					
		per cent	*per cent*	*mgm*			*seconds*		
9·05	Normal	40.8	19.5		2	180	0.08	−	Regular
9:30	III_{3-4}	42.0	20 8	29 6	3	220	0.08	−	Regular
10.00	III_{3-4}	43.1	20 8	28.0	5	210	0.09	+	Regular
10:11	IV	50.6	19.25	34 6	6	150	0.1	+	Regular
10.13	IV				7	130	0.11	+	Regular
10.15	IV				8	130	0.12	+	Regular
10·18	IV				9	100	0.14	+	Regular
10:19	IV				10		0.16	+	Partial block 2:1–3:1 with final arrest
10.19.5	IV	59.0	2 16		11				One P wave in 12 seconds; no ventricular action
10:20	Placed in respirator. Ventilation rate, 21 per minute								
10:20 5					12	50	0.1	+	Regular
10·21					13	50	0.1	+	Regular
10:22					14	130	0 13	+	Regular
10·24					15	70	0 16	+	Regular
10:30					16	180	0.08	+	Regular
10 40					17	220	0.08	+	Regular
10·45		28 3	18 3	38 8	18	160	0.08	+	Regular
11 00		26 6	17 0	44 7	19	110	0.12	−	Regular
11:20		28.0	14 4	45 5	20	90	0 2-0 36	−	Totally irregular with ventricular extrasystoles
11·21					20.5	50			Auriculoventricular nodal rhythm
11 21 5					21				Ventricular fibrillation
11 22					22				*Ventricular* fibrillation
11.24					23				Ventricular fibrillation

* Robbins and Baxter J Pharmacol and Exper Therap., 61, 162, 1937 (275)

† Stage III_{3-4} = Absence of wink reflex, muscular relaxation, and beginning failure of intercostal and diaphragmatic activity Stage IV = Respiratory arrest.

‡ + = Upright T wave, − = Inverted T wave.

See figure 10 for selected E K G records

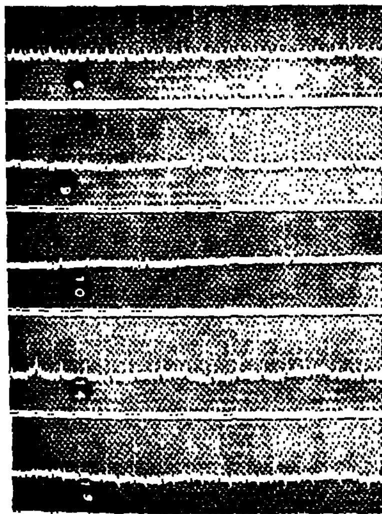


FIG 10 Electrocardiographic records from experiment 9 Consult table 16 for data which correlate the stage of anesthesia, arterial concentration of cyclopropane, oxygen, and carbon dioxide with the records shown in this figure Frequent U waves are present in E.K.G. number 9 (Robbins and Baxter: J Pharmacol & Exper. Therap , 61, 162, 1937)

were sectioned 20 minutes after the experiment was started. Electrocardiographic records are shown in figure 11.

The types of irregularities that developed during the period of respiratory arrest and in the presence of a low arterial oxygen content included nodal rhythm, ventricular extrasystoles, auriculoventricular block, and multiple focus ventricular tachycardia.

Table 17*

Experiment 17. The vagi were cut after the dog was anesthetized

Time	Stage	Arterial CO_2	Arterial O_2	Arterial C_2H_4	E K G Number	Rate	P-R Interval	T Wave	Rhythm
		per cent	*per cent*	*mgm.*			*seconds*		
8:50	Normal	42.5	19.5		1	105	0.12	+	Sinus arrhythmia
8:55.5	Induction				2	150	0.09	+	Regular
8:57	III_3				3	190	0.09	+	Regular
9:15	III_3				4	210	0.08	+	Regular—vagi cut 9:15.5
9:16	III_3				5	210	0.08	+	Regular
9:30	III_{3-4}	47.0	20.5	28.5	6	200	0.08	—	Regular
9:45	III_{3-4}			29.3	7	190	0.1	+	Regular
10:15	III_{3-4}	48.2	19.3	26.2	8	160	0.09	+	Regular
10:43	III_{3-4}				9	150	0.1	+	Regular
10:53	IV	60.0	11.3	34.2	10	160	0.08	+	Regular
10:55	IV				11	170	0.08	+	Regular
10:56	IV				12	110	0.1	+	Regular
10:56.5	IV				13	110	0.08	+	Regular
10:57	IV				14	110		+	Nodal
10:58	IV				15	130		+	Nodal with ventricular extrasystoles
10:59	IV	63.0	0.95		16	70		+	Nodal with ventricular extrasystoles
11:00	IV				17				Multiple focus ventricular extrasystoles
11:00	Placed in respirator. Ventilation rate, 21 per minute								
11:02					18	110	0.1	+	Regular
11:02.5					19	250	0.1	+	Regular
11:04					20	200	0.08	+	Regular
11:15		37.8	17.1	36.2	21	180	0.08	+	Regular
11:30				36.2	23	190	0.08	+	Regular
11:45				40.7	24	160	0.08	+	Regular
12:00		35.8	16.4	44.2	26	140	0.08	+	Regular
12:15				47.6	27	140			Nodal
12:30		32.4	10.6	50.7	29	140			Nodal
12:47		24.4	6.0	52.2	30	170			Nodal

* Robbins and Baxter. J. Pharmacol and Exper. Therap., 61, 162, 1937 (275). See figure 11 for selected E K G records

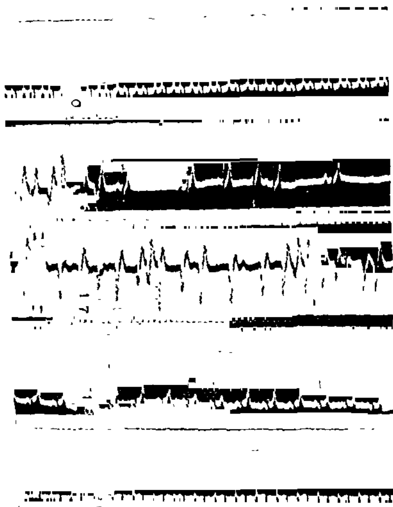


FIG 11 Electrocardiographic records from experiment 17. Consult table 17 for data which correlate the stage of anesthesia, arterial concentration of cyclopropane, oxygen, and carbon dioxide with the records shown in this figure. (Robbins and Baxter J Pharmacol & Exper Therap, 61, 162, 1937)

These returned to normal under artificial ventilation and an increased arterial oxygen and cyclopropane content. In the dogs with the vagi cut there was no record of auriculoventricular block nor was there any increase in the P-R interval during the period of respiratory arrest.

The average duration of respiratory arrest, before the onset of irregularities in those dogs which returned to normal cardiac func-

TABLE 17*

Experiment 17. The vagi were cut after the dog was anesthetized

Time	Stage	Arterial			E K G Number	Rate	P-R Interval	T Wave	Rhythm
		CO_2	O_2	C_3H_6					
		per cent	*per cent*	*mgm.*			*seconds*		
8:50	Normal	42.5	19.5		1	105	0.12	+	Sinus arrhythmia
8:55 5	Induction				2	150	0 09	+	Regular
8·57	III_3				3	190	0 09	+	Regular
9·15	III_3				4	210	0 08	+	Regular—vagi cut 9:15.5
9·16	III_3				5	210	0 08	+	Regular
9·30	III_{3-4}	47.0	20 5	28.5	6	200	0 08	−	Regular
9·45	III_{3-4}			29.3	7	190	0.1	+	Regular
10:15	III_{3-4}	48 2	19.3	26.2	8	160	0 09	+	Regular
10:43	III_{3-4}				9	150	0.1	+	Regular
10:53	IV	60 0	11 3	34 2	10	160	0.08	+	Regular
10 55	IV				11	170	0 08	+	Regular
10.56	IV				12	110	0.1	+	Regular
10:56.5	IV				13	110	0 08	+	Regular
10:57	IV				14	110		+	Nodal
10:58	IV				15	130		+	Nodal with ventricular extrasystoles
10.59	IV	63 0	0 95		16	70		+	Nodal with ventricular extrasystoles
11 00	IV				17				Multiple focus ventricular extrasystoles
11 00	Placed in respirator Ventilation rate, 21 per minute								
11 02					18	110	0 1	+	Regular
11:02 5					19	250	0 1	+	Regular
11:04					20	200	0 08	+	Regular
11:15		37 8	17 1	36 2	21	180	0 08	+	Regular
11:30				36 2	23	190	0 08	+	Regular
11:45				40 7	24	160	0 08	+	Regular
12:00		35 8	16 4	44 2	26	140	0 08	+	Regular
12:15				47.6	27	140			Nodal
12 30		32 4	10 6	50 7	29	140			Nodal
12 47		24 4	6 0	52 2	30	170			Nodal

* Robbins and Baxter J Pharmacol and Exper. Therap., 61, 162, 1937 (275). See figure 11 for selected E K G records

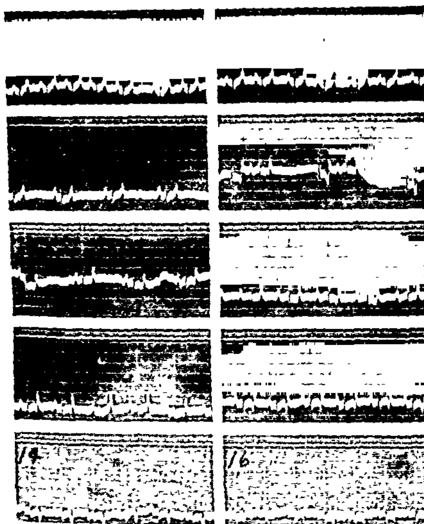


FIG. 13 Electrocardiographic records from experiment 20. See figure 12 and table 18 for further data.

arterial blood show that when artificial respiration is adequate, the cyclopropane content of the blood can be increased to a level about 30 per cent higher than that necessary for respiratory arrest while the heart remains normal. These data agree with those obtained in the studies of Seevers *et al.* on the concentrations of cyclopropane in the inspired air.

In these experiments the relation of the cardiac irregularities

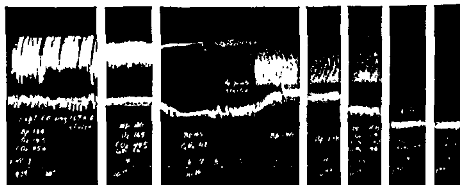


Fig. 12. Record of respiration and blood pressure from experiment 20. See figure 13 and table 18 for further data.

tion after artificial ventilation was instituted, was 4.8 minutes. In only one dog in this series was there any arrhythmia recorded before respiration ceased, and that was a few ventricular extrasystoles during induction in dog 18.

Figures 12 and 13 and table 18 show the blood pressure, blood gas concentrations, and electrocardiographic records from a dog treated as above except that blood pressure records were made in addition to the others. It is of interest to note that under artificial respiration the heart remained normal with an arterial content of 46.2 mgm. cyclopropane per 100 cc. of blood, whereas respiration ceased with a cyclopropane content of 31.2 mgm. per 100 cc. of blood.

From the above data, it seems that in dogs under cyclopropane anesthesia the heart is not adversely affected until the concentration has been so increased that respiration stops or is so diminished that a state of severe anoxemia exists, even though the anesthetic mixture in the bag contains adequate oxygen.

The arterial oxygen was considerably higher under deep anesthesia than in the control samples. Immediately after respiratory arrest, the arterial oxygen was 3 volumes per cent lower than normal; this, however, *rapidly declined until at the time of onset of* cardiac irregularities the arterial oxygen was only 2.8 volumes per cent.

The data regarding the cyclopropane concentrations in the

and Wastl (157), Koehler *et al.* (173), and Alexander and Himwich (4), in which anoxemia was produced by inspiring low concentrations of oxygen in nitrogen. This would indicate that the cyclopropane at this level is in no part responsible for the arrhythmias.

Part of the effects of anoxemia on the heart is due to stimuli from the medulla because there are some differences between the types of irregularities observed in dogs with vagi intact and those observed in dogs with vagi sectioned, the most marked differences being the lack of increase in the P-R interval and the absence of higher degrees of auriculoventricular block in the group with the vagi cut. Ventricular extrasystoles, nodal rhythm, and multiple focus ventricular arrhythmia were observed in each group at approximately the same degree of anoxemia; therefore, not all of the arrhythmias during respiratory arrest are of vagal origin.

During the period in which artificial respiration was maintained (average of 80 minutes), the concentration of cyclopropane was always above and on an average reached a level 30 per cent higher than that required for respiratory arrest, while the heart was still normal as shown by electrocardiographic records. Adequate oxygenation permits this increase. However, even though the arterial oxygen is adequate and carbon dioxide decreases, if the cyclopropane is increased sufficiently, cardiac arrhythmias and failure result, probably due to direct action of the drug on the heart.

CARDIAC ARRHYTHMIAS AND HIGH CONCENTRATION OF CYCLOPROPANE

Lee and his associates (181) in the study on the mechanism of production of cardiac irregularities with high concentrations of cyclopropane have reported some very interesting work. They studied the effect of concentrations of thirty-eight to eighty per cent cyclopropane in oxygen upon a large series of dogs, determining the various cardiac arrhythmias that were produced and at the same time determining the concentration of cyclopropane as well as oxygen in the blood. The dogs were placed on the concentrations up to 65 per cent cyclopropane from 30 to 60 minutes

TABLE 18

The effect of artificial respiration, after respiratory arrest produced by cyclopropane, upon the heart rate, rhythm, and blood pressure

Experiment 20 Dog, 13.7 kgm., ♂—5/14/37

Time	Procedure or Stage	Blood Pressure	EKG Analysis				
			No	Rate	P-R	T	Rhythm
9.30	Control	130	1*	120	.11	+	S. A.
9·35	C_3H_6 on						
9:36		134	2	130	.12	+	S. A.
9:42		126	3	110	.12	+	Regular
9.57	III_{3-4}	132	4*	110	.12	+	Regular
10·27	III_{3-4}	136	5	110	.12	+	Regular
10.36	IV	105	6*	60	14	+	Regular
10:37	IV						
	Respirator started						
10 39	IV	140	10*	85	.2	+	Regular
10.43	IV	138	11*	85	.16	+	Regular
11·15	IV	108	13*	95	.14		Regular
11:30	IV	76	14*	95	.15		Regular
11:46	IV	70	16*	110	.14		Regular

* See figure 13 for electrocardiographic records See figure 12 for records of blood pressure and respiration

to the very low arterial oxygen after respiratory arrest is striking. The degree of anoxemia present at the onset of the irregularities is severe We are of the opinion that the cardiac irregularities which develop during this period of respiratory arrest are due not to any effect of cyclopropane on the heart, but to the extreme degree of anoxemia. This conclusion is based upon two points: first, under artificial respiration we are able to build up a much higher blood cyclopropane concentration without cardiac arrhythmias; and second, Greene and Gilbert (116), Mathison (203), and Resnick (266) have noted irregularities similar to those observed here in their studies of anoxemia in relation to blood pressure and electrocardiographic changes. It is of interest to note that the arterial oxygen concentrations at the time of onset of cardiac irregularities in these experiments with cyclopropane are no higher than those observed in the experiments by Jarisch

animal was placed in a respirator and given artificial respiration by that mechanism while the cyclopropane in the inspired air was being increased. It seems quite certain then that cyclopropane can and does produce *cardiac arrhythmias of spontaneous origin* in the dog heart providing the concentration of cyclopropane in the inspired air is as great or twice as great as that necessary to produce respiratory arrest. Two lines from the summary of Lee *et al.* are given: "From the results of these studies it is apparent that cardiac irregularities are aroused spontaneously in the dog when the depth of cyclopropane anesthesia approaches respiratory arrest."

Studies on Cats

Stutzman and Pettinga (321, 7) reported a study on the mechanism of cardiac arrhythmias during anesthesia using the cat as the experimental animal. They found that by removing part of the abdominal viscera, the adrenals, the splanchnic nerves up to T-10, arrhythmias were abolished. They thought that afferent impulses in the abdominal viscera were set off by cyclopropane which caused efferent impulses via T-1 to T-5 to the heart to produce irregularities; Allen and his associates blocked the irregularities by cardiac sympathectomy. On the basis of their work and the work of Allen, they believe that cyclopropane works by a reflex mechanism upon the cat heart.

In 1945, Allen and his associates (5) reported some studies upon the influence of the autonomic nervous system upon spontaneous cardiac arrhythmias during cyclopropane anesthesia. In the cat, spontaneous cardiac arrhythmias occur very frequently in the lighter planes of anesthesia, and it is not essential for the production of these arrhythmias to carry the animal to the plane of respiratory arrest or to introduce some factor as morphine or epinephrine. Allen and his associates set out with the intention of showing the effects of the vagus and vagotomy and the effect of the sympathetics and sympathectomy on cardiac arrhythmias. In a series of 20 cats anesthesia was produced *with cyclopropane* and the electrocardiographic changes observed. In 15 of the 20

TABLE 19

*Cardiac irregularities arising during controlled respiration with cyclopropane-oxygen mixtures of known concentration, as determined by chemical analysis**

Cyclopropane in Anesthetic Mixture	Average Time of Administration	Number of Animals	Auriculoventricular Nodal Block	A-V Extrasystole	A-V Nodal Rhythm	Ventricular Extrasystole	Slow Ventricular Rhythm	Ventricular Tachycardia	Ventricular Fibrillation	Cardiac Depression
per cent	*minutes*									
38 to 44	60	12				2				
45 to 54	45	15	4		5	7		2		1
55 to 64	30	16	8	3	4	11	6	2	2	
65 to 80	15	14	13	1	10	9	6	7	4	4

* The amount of cyclopropane in the mixture is shown in the first column at the left and the average time of administration of the various percentages is indicated in the second column. There was increased severity of irregularities with increasing cyclopropane percentages. Only one anesthetic mixture was tested on any animal in a day

Lee *et al.*: Anesthesiology, 4, 489, 1943 (181).

and from 65 to 80 per cent cyclopropane for only 15 minutes. These animals had an endotracheal tube with an inflated cuff in place and were given artificial respiration with these high concentrations just as soon as it was evident that their own respiratory mechanism was beginning to fail. Part of the results of their studies is shown in table 19.

It is interesting to note that as long as they stayed on a concentration of cyclopropane that was in the range which produced respiratory arrest in man, as quoted by Waters and Schmidt (341), cardiac arrhythmias were observed in only two of twelve animals, and these were ventricular extrasystoles. As soon as the concentration was anywhere from 3 to 12 per cent higher than their average, cardiac arrhythmias increased very greatly. As the concentration was increased further, the frequencies of arrhythmias were greater and more severe types were observed. The highest concentration of cyclopropane in the blood observed was 58.9 mgm. per 100 cc. and this was at a time in which the oxygen concentration was adequate. This value is 5 mgm. per 100 cc. higher than any of those obtained by Robbins in his work in which the

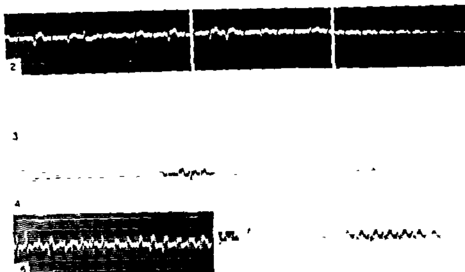


Fig. 14 Effect of amytal sodium upon the arrhythmia in the cat under cyclopropane anesthesia Arrhythmias were present in each of the four cats at the time of injection of amytal as shown on the left side of the figure, and the rhythm returned to normal within 20 seconds or less as shown in the right side of the figure.

Cat	*Weight*	C_3H_6	*Amytal mgm/kgm*	*Duration of Reg. Rhythm min.*
2	2.7	19.2	10	10
3	2.6	33	10	3
4	3	32	8	2
5	1 6	20 6	10	2

(Robbins unpublished data (269))

of these cats was there a return to normal rhythm as a result of the administration of atropine in this size dose. We have suggested throughout that the preanesthetic medication to reduce or prevent the frequency of cardiac arrhythmias during cyclopropane anesthesia should be a barbiturate. This has been shown as a result of our studies in the dogs and now is supported by results in these cats.

We carried out some further studies to investigate the possible effect of thoracotomy alone and thoracotomy with bilateral sympathectomy upon the arrhythmias. It is not possible from the paper of Allen and his associates to determine whether or not

animals, cardiac arrhythmias, either ventricular tachycardia, multiple ventricular extrasystoles or auriculoventricular tachycardia, were observed. After bilateral vagotomy, ventricular arrhythmias were observed in 19 of the 20 cats. Upon thoracotomy and removal of the thoracic sympathetic chain from the stellate to the sixth thoracic ganglia bilaterally, the rhythm returned to normal immediately in 17 of the 20 cats, and in three, A-V nodal rhythm was present part of the time during the investigation In a further series of 10 cats, bilateral sympathectomy was done first. In 9 of these 10 cats, ventricular rhythms were present as a result of the anesthetic. Upon thoracotomy with bilateral removal of the sympathetic chain from the stellate to the sixth ganglion there was a return to the normal sino-auricular rhythm in 7 cats, and when the vagi were cut later, two of the ten cats still persisted in ventricular rhythm or an A-V nodal rhythm. As a result of these studies on the 30 cats, they were of the opinion that the cardiac arrhythmias could be prevented routinely or almost routinely by sympathectomy and that bilateral vagotomy had no effect whatsoever upon the arrhythmia.

We (269) had been interested in this same problem and studied the effect of barbiturates upon the spontaneous arrhythmia in the cat during cyclopropane anesthesia. In a series of five cats, an attempt was made to determine the effect of amytal upon the cardiac arrhythmias produced by cyclopropane under moderately deep anesthesia The concentration of cyclopropane in the blood at the time of the injection of amytal was determined and recorded in these experiments. The doses of the amytal varied from 2.5 to 10 mgm. at a single injection but in no animal was more than 17.5 mgm. per kilo administered. In each of four animals that received as much as 8 mgm. per kilo at a single dose, cardiac arrhythmias were returned to normal during the recording of the electrocardiographic pattern on the electrocardiogram within twenty to thirty seconds following the injection as shown in figure 14 and remained normal for two to ten minutes. In two instances, atropine .2 mgm. per kilo was given intravenously, and in neither

TABLE 20

Effect of thoracotomy and thoracic sympathectomy stellate to sixth ganglion upon the spontaneous arrhythmia in the cat under cyclopropane anesthesia

Experiment 7. Cat 3 K

Date	Time	Stage	C_3H_6, mgm./100 cc.	E K G ±±	Rate	Rhythm*
7/8	9:30	C_3H_6 on				
	9:45	Tube in				
	10:00	III_3		2	204	VEX; Nodal
	10·15	III_3—Lt chain out		3	168	SA; occ. VEX
	10:35	III_3—Lt. thorax closed		4	180	SA Reg
	10·50	III_3—Rt. chain out		5	150	SA Reg.
	10:57	III_3—Rt thorax closed		6	140	SA Reg.
7/25	9·00	Control		1	132	SA Reg.
	9:01	C_3H_6 on				
	9·10	III_3		2	96	SA Reg.
	9:15	III_{2-3} tube in				
	9:25	III_{2-3}		4	252	VEX; Nodal
	9:35	III_3	19	5	252	VEX; Nodal
	9:50	III_3 (amytal 10 mgm./kgm.)	19	6	192 216	SA; VEX—Nodal SA Reg.
7/30	10·55	Control		2	156	SA Reg.
	11:00	C_3H_6 on				
	11 15	III_{2-3} tube in		3	264	VEX; Nodal
	11·25	III_{2-3} (amytal)	19 2	4	240 228	VEX; Noda. SA Reg.
	11.45	III_4 (amytal)	20	7	214 240	VEX; Nodal SA Reg.
	11.55	III_4		9	228	SA Reg.
8/6	10.00	Control		1	132	SA Reg.
	10.05	C_3H_6 on				
	10 10	III_2		2	66	SA Reg
	10 17	III_2		3	216	SA; VEX; Nodal; Tot irreg.
	10·40	III_3	19.2	4	264	Bigem.; VEX—Nodal

* SA = sino-auricular rhythm; Nodal = AV Nodal; VEX = ventricular extrasystole, Tot. irreg = total irregular; Bigem = bigeminal rhythm.

See figure 15 for selected E.K G records

these were acute experiments or chronic experiments in which the animals were permitted to recover, but comments by Allen indicate that they were acute experiments in which the study of the influence of sympathectomy and vagotomy was ended soon after the sympathectomy or vagotomy, whichever occurred last in their study.

In our study upon the effect of thoracotomy or thoraotomy plus sympathectomy upon the cardiac pattern in the cat, nine animals were used. Our procedure was to put the animals to sleep with cyclopropane, place an endotracheal tube and carry them on the closed system during the operative procedure. Electrocardiographic records were made in the plane 2 or 3 of surgical anesthesia before the operation was started, and then the thoracotomy was done under clean technic with records of the heart after thoracotomy, with records after the sympathectomy on each side and then records immediately before closure as well as records after closure; these animals were permitted to recover and studies made upon them later. In addition to careful dissection and identification of sympathetic ganglia from the stellate down through the fifth or sixth on both sides, we observed, after the animal recovered, the size of the pupil as an indication at least of sympathectomy of the upper portion of the thoracic chain. In two cats, studies were made of the cardiac rhythm before and after anesthesia and after opening both sides of the chest on one cat, and one side in the other, but without touching any of the viscera or handling or dissecting the sympathetic system, otherwise a pure thoracotomy. In each cat positive pressure respiration was maintained and the chest kept open for thirty-five minutes during which time frequent electrocardiographic records were made. At the end of this time, the thoracotomy was closed and records of the heart pattern made for ten to fifteen minutes. The mechanism by which the cardiac rhythm was returned to normal as a result of open thoracotomy and sympathectomy or open thoracotomy alone is not clear at the present time, unless possibly due to an improved elimination of carbon dioxide, but in eight of the nine cats

TABLE 22

The effect of unilateral thoracotomy alone on spontaneous cardiac arrhythmia in the cat under cyclopropane anesthesia

Experiment 13 Cat 3 K

Date	Time	Stage	C_3H_6, mgm per 100 cc. Blood	E K G	Rate	Rhythm
8/8	10:05	Control		1	216	SA Reg.
	10:06	C_3H_6 on				
	10:10	III_2		2	228	Nodal; VEX
	10:25	III_3			288	Nodal; VEX
	10.35	III_{2-4}	29	5	252	Nodal; VEX
	10:40	III—Rt. thorax open				
	10.43	III		6	156	SA Reg.
	10:50	III_{3-4}	24	9	132	SA Reg.
	11·10	III_{3-4}	22	11	156	SA Reg.
	11:15	Rt. thorax closed		12	138	SA Reg.
	11·22	III_4	26	13	192	Nodal; VEX
	11:35	III_4	22	14	168	Nodal; VEX
	11:36	C_3H_6 off				
	11·45	Awake		15	204	SA Reg.

See figure 17 for selected E K G records.

mgm. per 100 cc. up to a high of 24 to 26 mgm. per 100 cc. There seems little question but that the thoracic sympathectomy has no effect upon the frequency of the spontaneous cardiac arrhythmias observed in the cat during cyclopropane anesthesia, and that thoracotomy alone may give a temporary protection as long as the chest is opened. Protocols of three experiments and electrocardiographic records of these experiments are shown below in tables 20, 21, and 22 and figures 15, 16, and 17. A summary table 23 shows data in each of the nine experiments. In only one cat with a thoracotomy and sympathectomy was there a failure to revert the rhythm to normal.

EFFECT OF CYCLOPROPANE ON THE IRRITABILITY OF THE AUTOMATIC TISSUE

Betlach (22), in studying the effect of ether, cyclopropane, pentothal, and amytal on the heart as shown by electrocardio-

that had a thoracotomy plus a sympathectomy or thoracotomy alone, these procedures restored normal rhythm during the thoracotomy. In three cats in which bilateral thoracic sympathectomy had been done, studies were made from seven to twenty-five days after the sympathectomy upon the effect of cyclopropane anesthesia on the cardiac rhythm. In each of seven experiments upon these three cats, cardiac arrhythmias of all types were observed during plane 2 to 3 of surgical anesthesia, and at times in which the concentration of cyclopropane in the blood varied from a low of 19

TABLE 21

Effect of thoracotomy alone on spontaneous cardiac arrhythmias in the cat under cyclopropane anesthesia

Experiment 12. Cat 1 9 K

Date	Time	Stage	C_3H_6, mgm per 100 cc Blood	E K G	Rate	Rhythm
8/7	10 25	Control	*	11	180	SA Reg.
	10 30	III_2		12	90	SA Reg
	10 32	Tube in				
	10 35	III_3		13	72	SA Reg.
	10.36	III_3		14	168	SA; Nodal; VEX
	10 55	III_{3-4}	48	15	90	SA Reg
	11 10	III_4	65	16	264	Nodal; VEX; Bigem
	11 17	Rt thorax open				
	11 20	III_4		18	120	SA with 3 VEX
	11 22	Lt thorax open				
	11 30	III_4	65	19	132	SA Reg
	11 40	III_4	58	21	132	SA Reg.
	11 52	Rt thorax closed		22		SA Reg
	12 02	Lt thorax closed		23	120	SA Reg
	12 10	III_4	67	24	120	SA Reg.
	12 14	III_4		25	114	SA; VEX
	12 17	III_4	58	26	216	Nodal; VEX, Tot irreg
	12 20	C_3H_6 off				
	12.30	Awake		29	114	SA Reg

* The high values for cyclopropane in the blood of this cat is due to the high fat content of the blood of this particular cat

See figure 16 for selected E K G records

Cat 11 8/2	108	SA	240	Nod		120 Reg.	120 Reg.	
Cat 12 8/7	180	SA	168	Nod., VEX; Tot irreg.	120 Reg.	Reg.; No symp.	Reg.; No symp.	Irreg. in 10′ after closure
Cat 13 8/8	216	SA	240	Nod ; VEX	144 Reg.	Regular for 30′ with lt. thorax open		Irreg. in 7′ after closure
Cat 14	192	SA	288	VT; Nod.; VEX	204 Nod.; VEX	240 SA; VEX	192 SA; VEX	Nod.; VEX

TABLE 23

Effect of thoractomy and sympathectomy or thoracotomy alone upon the spontaneous cardiac arrhythmia in the cat under cyclopropane anesthesia

Expt Date	Control		III_{2-3}		Chest Open & Art Resp			Chest Closed	
	Rate	Rhythm	Rate	Rhythm	Before symp	After 1st symp	After 2nd symp	Reg	Irreg
Cat 6									
7/9		SA		Nodal, MFVEX	MFVEX	MFVEX	Reg.		Nod.; MFVEX
7/17		SA	192	VEX, Tot irreg					
7/27	96	SA	132	VEX, Nod.					
8/3	78	SA	204	VEX, Tot irreg					
Cat 7									
7/18		SA		VEX; Nod.		168 SA	150 Reg.		
7/25	132	SA	252	VEX; Nod.					
7/30	156	SA	264	VEX; Nod.					
8/6	132	SA	216	SA; Nod ; VEX					
Cat 8									
7/23		SA	252	SA, Nod.; VEX	216 SA; Nod.; VEX	216 SA; Nod.; VEX	156 Reg.		
8/2	140	SA	240	Nod ; VEX					
Cat 9									
8/1	180	SA	144	Nod.	132 Nod.	120 Reg.			Nod.; VEX
Cat 10									
8/1	150	SA	180	Nod.; VEX			150 Reg	Could not revive	

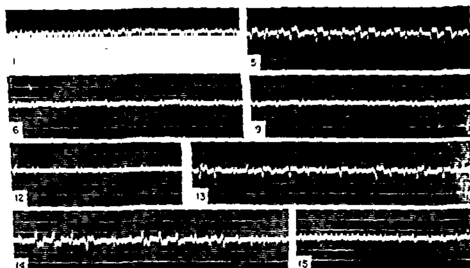


FIG. 17 Electrocardiographic records from experiment 13 described in table 22

Meek, Hathaway, and Orth (210) have studied the effects of the injection of epinephrine hydrochloride (.01 mgm. per kilogram in 5 cc. of saline, injected over a period of 50 seconds) upon the heart rate and rhythm in trained unanesthetized dogs. After adequate control studies were made, the same dogs were anesthetized to stage III$_2$ and III$_4$ with cyclopropane, chloroform, and ether on different days and the same amount of epinephrine hydrochloride injected as in the awakened state. Continuous electrocardiograms were made during and after the injections until the heart returned to normal. The data from these studies are shown in table 24 and figure 18.

The table presents some very interesting data in that in only seven of the twenty experiments under ether were abnormal changes produced by the injection of epinephrine hydrochloride, and these were all nodal tachycardias of short duration; the absence of arrhythmias resulting from escape phenomenon is due to the fact that ether depresses the vagal action both centrally and peripherally. The absence of ventricular fibrillation in the dogs under chloroform after the injection of epinephrine is unexpected because of the ease with which it was produced in cats by Levy (184) and the ease with which Douglas (86, 87) was

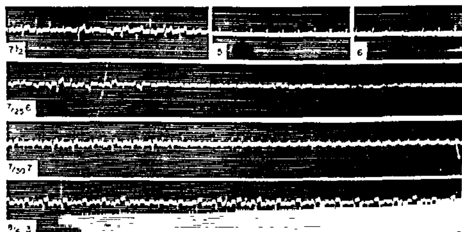


FIG. 15. Electrocardiographic records from experiment 7 described in table 20

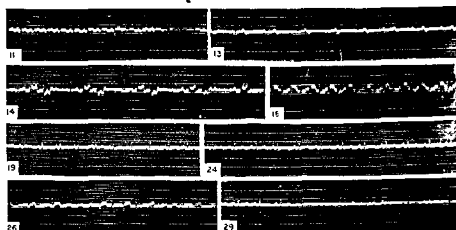


FIG 16 Electrocardiographic records from experiment 12 described in table 21

grams, found that ether and cyclopropane anesthesia produced ventricular extrasystoles but that amytal or pentothal did not cause any abnormal changes

In some 40 non-premedicated dogs in which we have made electrocardiographic records during anesthesia with cyclopropane, we have observed or recorded irregularities in only three before intercostal paralysis and one of these occurred during rapid induction (277).

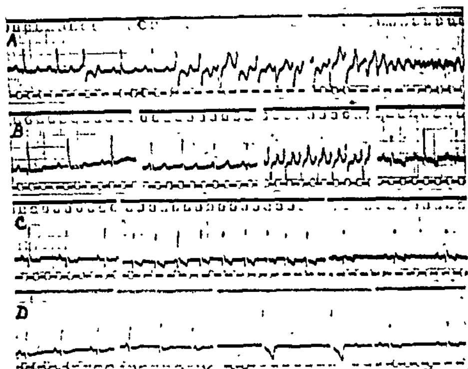


FIG 18 Arrhythmias observed after the injection of the test dose of adrenalin in cyclopropane and chloroform anesthesias

A. Deep cyclopropane Scattered premature beats are followed by ventricular tachycardia and this passes into ventricular fibrillation. B. Deep cyclopropane. A-V nodal rhythm appears which is followed by ventricular tachycardia and later by recovery C Light chloroform A rapid A-V nodal rhythm is followed by recovery D Deep chloroform A-V nodal rhythm is followed by complete A-V heart block and a slow independent ventricular rhythm (After Meek, Hathaway, and Orth J. Pharmacol & Exper. Therap , 61, 240, 1937)

However, when no adrenalin was injected we were able to keep all the animals studied in surgical anesthesia with a normal heart rhythm. Their ability to withstand further strain was, however, definitely lessened. On the other hand, cyclopropane has a certain advantage over many anesthetics in that the tissues may be saturated and desaturated quickly The fundamental data, at the present moment, are not abundant enough to justify one in determining the exact value of cyclopropane as an anesthetic agent.

Their evidence convinces one that cyclopropane increases the irritability of the automatic tissues of the heart in dogs more than chloroform or ether. The size dose of epinephrine used is only twice the amount that Cannon (58) estimates could be

TABLE 21*

Showing the cardiac effects of the test injection of adrenalin on animals which had been under the anesthesia indicated for 30 minutes or more

Ten of the animals were carried through the entire series. Repeated tests under the same condition showed almost exact duplication of results

Anesthesia	Number of Animals	Initial Rate Increased	Initial Rate Decreased	A-V Block	Nodal Extrasystoles	Ventricular Extrasystoles	Nodal Rhythm	Slow Ventricular Rhythm	Ventricular Tachycardia	Ventricular Fibrillation	Average Length of Tachycardia
											seconds
Controls	17	6	11	12	14	10	9	5	1	0	
Light ether	10	8	0	0	0	0	3	0	0	0	
Deep ether	10	6	0	0	0	0	4	0	0	0	
Light chloroform	10	5	0	4	0	5	4	3	1	0	28 0
Deep chloroform	10	6	2	7	0	8	2	5	2	0	22 0
Light cyclopropane	17	14	3	2	5	11	5	0	11	1	19 0
Deep cyclopropane	17	14	1	0	1	13	5	0	16	1	44.5
Deep cyclopropane with premedication	10	9	0	0	1	9	3	0	9	0	48.0
Deep chloroform with respiratory arrest. No *adrenalin*	4			2	*0*	*0*	2	4	*0*	*0*	

* After Meek, Hathaway, and Orth· J Pharmacol and Exper. Therap., 61, 240, 1937 (210)

able to produce it in dogs. The increased frequency of arrhythmias of the more severe types (ventricular tachycardia and ventricular fibrillation) and the long duration of these in dogs under cyclopropane are of great interest. A paragraph from their comments is quoted below:

> Cyclopropane, as judged by our standard injection of adrenalin, has a more marked stimulating or sensitizing effect on the ventricular automatic tissue than either chloroform or ether Chloroform ranks second and ether third. This may not mean that cyclopropane is a dangerous anesthetic agent, for almost any pharmacological agent has some undesirable side effect It certainly does mean that great attention must be given the heart during a cyclopropane anesthesia.

the sino-auricular rate. Under chloroform some cardiac sensitization was shown to cobefrin and arterenol, less to ephedrine, and none to neosynephrin.

In a later paper Orth *et al.* (243) have reported in detail the work which was quoted above in summary. Five of twenty dogs anesthetized with cyclopropane developed ventricular fibrillation after the injection of epinephrine HCl, .01 mgm. per kilogram, whereas in eighty other dogs under cyclopropane anesthesia the injection of other sympathomimetic amines, in doses that produced a rise of blood pressure equal to that produced by the dose of epinephrine HCl, developed ventricular fibrillation in only two dogs. These results are shown in table 25.

Orth and his associates, in a further study on the relationship of chemical structure of sympathomimetic amines to ventricular tachycardia during anesthesia in which fifteen drugs were added to their original eleven, show that six primary and secondary amines with the catechol nucleus produce ventricular tachycardia when given in doses producing the same rise of blood pressure as that observed following the administration of epinephrine. Tertiary amines with the catechol nucleus and other amines do not produce these cardiac arrhythmias.

Likewise, Murphy and his associates (226), in a study on the effect of aliphatic sympathomimetic amines on cardiac automatic tissues in dogs under cyclopropane in which eighteen amines were studied, found that with six there was no ventricular tachycardia produced with dogs under anesthesia with a dose that produced a rise in blood pressure equal to that of the standard dose of epinephrine. However, with eleven of these compounds there was observed extrasystoles and ventricular tachycardia when the dose of the drug produced an increase in blood pressure equal to that of the standard dose of 0.01 mgm. per kilo of epinephrine. All of the aliphatic amines studied that gave rise to an increased blood pressure also gave rise to sino-auricular tachycardia.

In a later study by Stutzman and his associates (322) upon twenty-six primary and secondary amines, it was observed that

liberated by the maximal reflex stimulation of the sympathetic system. Whether or not cyclopropane increases sympathetic activity is not definitely shown.

Orth, Stutzman, and Meek (245) have reported the effects of numerous sympathomimetic amines upon the heart of dogs under ether, cyclopropane, and chloroform. An abstract of their report is given below:

Dogs were maintained until equilibrated on mixtures of ether, chloroform, or cyclopropane, diluted with oxygen, and sufficient to produce deep surgical anesthesia. Various sympathomimetic amines (adrenalin, ephedrine, propadrin, benzedrine, cobefrin, kephrine, epinine, paredrine, arterenol, synephrin and neosynephrin) in doses equivalent in blood pressure raising power to 0 01 mgm per kgm of adrenalin were diluted with Locke's to a standard volume and injected intravenously at a standard rate. Electrocardiograms (lead II throughout) of the arrhythmias resulting allowed the determination of the stimulating or sensitizing effect of each of the anesthetic agents on the autonomic tissues of the dog's heart.

Information regarding the active group in the molecules of the amine; the effect of premedication by some of the barbiturates, and evidence as to whether the cardiac effects under cyclopropane are due to the direct action of the agent or to an accompanying anoxemia, has been obtained

Cyclopropane greatly enhances the activity of adrenalin on the automatic tissues of the dog's heart. In controls adrenalin produces only escape phenomena but under the anesthetic multifocal ventricular tachycardia occurs in practically all experiments Adrenalin is therefore contraindicated in cyclopropane anesthesia Comparable pressor doses of arterenol, epinine, cobefrin, and kephrine acted similarly to adrenalin on the ventricular automatic tissue in cyclopropane anesthesia Cyclopropane sensitizes the ventricular automatic tissue to those sympathomimetic amines with the catechol nucleus. Ephedrine, paredrine, benzedrine, propadrin, synephrin, and neosynephrin do not, in comparable pressor dosages, exert such effects in cyclopropane anesthesia However, all but neosynephrin markedly accelerate the sino-auricular rate. In the dog under cyclopropane, neosynephrin is the sympathomimetic amine most favorable to the heart Anoxemia was not a factor in the sensitization Premedication with sodium barbital, amytal, or nembutal gave no protection against cardiac sensiti ation from cyclopropane

In ether anesthesia neither ephedrine, arterenol, cobefrin, nor neosynephrin produced ventricular tachycardia Presumably then ether does not sensitize the heart to any of the common types of amines All except neosynephrin increased

with only two there were no undesirable effects produced. These two drugs were methoxamine and phenylephrine.

Cummings and Hays (79) have reported studies of adrenergic and ganglionic stimulating drugs administered during cyclopropane. They observed in thirty-six dogs under cyclopropane anesthesia, 16 per cent, that 1.98 micrograms per kilo induced ventricular extrasystoles in all animals, whereas in dogs under ether anesthesia ten times this amount of the drug did not produce cardiac arrhythmias. In dogs, phenylephrine, methoxamine, and naphazoline, in doses which gave vasopressor response equal to that of the standard dose of epinephrine, failed to cause cardiac arrhythmias. Thus they feel that cardiac arrhythmia is not due to or is not necessarily a result of the hypertension that is produced by the sympathomimetic amines, as is thought in some instances by Moe and his associates (103).

Decerebration and arrhythmias. Allen and his associates (8), in their study on the production of ventricular tachycardia by epinephrine on decerebrate animals, in which decerebration had been produced by the anemic technique, found that in fourteen of fifteen experiments the standard dose of adrenalin did not produce cardiac arrhythmias. With doses of three to thirty times the stardard dose they found ventricular tachycardia in some instances. They conclude, therefore, that the intact mid brain is necessary for the production of cardiac arrhythmias under cyclopropane anesthesia by the injection of adrenalin. Likewise, by the removal of the stellate and 2nd to 6th thoracic ganglia in two dogs, they were able to prevent the arrhythmias on the injection of epinephrine. From these studies they conclude that cyclopropane stimulates the brain centers and also has a direct action on the heart.

Thyroid and cardiac arrhythmias. In subsequent studies by Stutzman and Meek (319) upon the role of thyroid in cyclopropane-adrenalin tachycardia, the duration of the ventricular tachycardia after the intravenous administration of the test dose of epinephrine to normal dogs was used as a standard of compari-

TABLE 25*

Cardiac arrhythmias resulting from injection of blood pressure raising drugs in doses equal in effectiveness to 0.01 mgm. of adrenalin per kilogram during surgical cyclopropane anesthesias

Procedure	*Dosage*	Number of Animals	A-V Block	A-V Nodal Extrasystoles	Ventricular Extrasystoles	Nodal Rhythm	Slow Ventricular Rhythm	Ventricular Tachycardia	Ventricular Fibrillation	Sino-auricular Tachycardia
	mgm per kgm									
Adrenalin control	0.01	19	10	12	7	15	5	3	0	0
Adrenalin with cyclopropane	0.01	20	1	9	10	7	0	20	5	17
Ephedrinecontrol	4 0	13	9	9	8	8	5	1	0	0
Ephedrine with cyclopropane	4.0	13	0	0	10	5	0	2	0	13
Propadrin control	3 0	11	10	5	5	4	5	0	0	1
Propadrin with cyclopropane	3 0	10	0	0	3	0	0	0	0	8
Benzedrine control	5 0	11	1	6	4	2	0	0	0	2
Benzedrine control	*5 0*	*10*	*1*	*0*	*1*	*1*	*0*	*1*	*0*	10
Cobefrin control	0.025–0.05	11	6	6	5	7	4	1	0	0
Cobefrin with cyclopropane		10	0	2	4	6	1	10	1	3
Kephrine control	1.0	4	2	3	2	3	1	0	0	0
Kephrine with cyclopropane	*0 50–0 75*	*4*	*0*	*0*	*4*	*2*	*0*	*4*	*0*	4
Epinine control	0 10	6	2	1	2	4	0	0	0	0
Epinine with cyclopropane	0 10	7	0	0	6	5	0	7	1	5
Paredrine control	0 75–1 0	8	1	5	2	6	0	0	0	0
Paredrine with cyclopropane		7	0	1	3	0	0	1	0	5
Arterenol control	0 01	6	2	5	2	5	4	0	0	0
Arterenol with cyclopropane	0 01	5	1	1	4	3	2	4	0	2
Synephrin control	3 0–5 0	6	2	2	5	1	3	0	0	0
Synephrin with cyclopropane		4	0	0	3	1	0	0	0	4
Neosynephrin control	0 05	10	4	3	5	2	1	1	0	0
Neosynephrin with cyclopropane	0 05	10	0	0	1	0	0	0	0	0

* Orth *et al* J. Pharmacol and Exper Therap , 67, 1, 1939 (243).

mechanisms other than these that were responsible for the benefit which they obtained when this operative procedure was carried out.

Potassium and cardiac arrhythmias. Two of the most interesting studies arising from the laboratories at the University of Wisconsin were those by O'Brien and his associates (238) upon the effect of sympathomimetic amines on arterial plasma potassium and cardiac rhythm in anesthetized dogs. They measured the change in arterial potassium after epinephrine in dogs under cyclopropane anesthesia, under pentobarbital sodium, and under ether, and in the awakened state, and after dihydroergotamine and dibenamine administration. They observed in the dogs under cyclopropane that there was an increase in the potassium of approximately 100 per cent, and in all of these animals ventricular tachycardia was noted. When dihydroergotamine and dibenamine were administered, then a subsequent administration of epinephrine failed to produce a rise in arterial potassium and also prevented the ventricular tachycardia and kept the blood pressure on a normal or constant state. They believe then that by some mechanism epinephrine under cyclopropane causes a liberation of potassium which in turn causes the cardiac arrhythmias.

In a more recent study by O'Brien and his associates (237) on the effect of the elimination of the hepatic circulation on cyclopropane-epinephrine ventricular tachycardia and arterial potassium in dogs, they have reported the following observations. In eleven control dogs, ventricular tachycardia and a rise of potassium of 16.5 mgm. were observed upon the administration of .005 mgm. of epinephrine per kilo over a fifty second period. In a group of eighteen dogs in which there was a porto caval shunt and ligation of the hepatic artery, thus excluding the hepatic blood flow, there was complete protection in seventeen of the eighteen dogs and almost complete absence of the potassium changes that were ordinarily produced by epinephrine.

They believe now that cyclopropane anesthesia stimulates the

son of the effect of thyroid upon the irritability. It was observed in eleven control dogs that the duration of the tachycardia was fifty-two seconds at a time when the dogs used an average of 125 cc. of oxygen per sq. meter per minute. In the animals that were hypothyroid as indicated by reduction of 33 per cent in their oxygen utilization, the duration of the tachycardia was only sixteen seconds in six of the eleven dogs that showed a tachycardia. In eleven dogs that were hyperthyroid as indicated by oxygen consumption of 58 per cent above the control, the administration of the standard dose of adrenalin produced a tachycardia of 83 seconds. Thus they feel that the thyroid hormone increases the sensitivity of the heart to cyclopropane and epinephrine.

Digitalis and cardiac arrhythmias. Stutzman and his associates (316) report a study of the response of digitalized heart to cyclopropane-epinephrine in the dogs. They found that the type *of arrhythmia observed is much more severe in these animals* and that the duration of the arrhythmia is greater in the animals that had had digitalis than in the control animals.

More recently the studies from the laboratory at the University, of Wisconsin have been along the line of trying to observe what portion of the body is necessary and essential in the production of these cardiac arrhythmias upon the administration of epinephrine during cyclopropane anesthesia. In 1947, Stutzman and his associates (320–321), by the removal of certain portions of the sympathetic system in the abdomen, particularly that in the mesentery of the upper part of the small intestine, found that there were no arrhythmias following the administration of epinephrine under cyclopropane anesthesia. They felt that stimuli from this area were sent up by afferent fibers in the sympathetic system to the brain and were returned again to the heart by way of the sympathetic system to sensitize the heart against cyclopropane. What part possible trauma or shock had in producing this protection is not quite clear, but later experiments showed

mechanisms other than these that were responsible for the benefit which they obtained when this operative procedure was carried out.

Potassium and cardiac arrhythmias. Two of the most interesting studies arising from the laboratories at the University of Wisconsin were those by O'Brien and his associates (238) upon the effect of sympathomimetic amines on arterial plasma potassium and cardiac rhythm in anesthetized dogs. They measured the change in arterial potassium after epinephrine in dogs under cyclopropane anesthesia, under pentobarbital sodium, and under ether, and in the awakened state, and after dihydroergotamine and dibenamine administration. They observed in the dogs under cyclopropane that there was an increase in the potassium of approximately 100 per cent, and in all of these animals ventricular tachycardia was noted. When dihydroergotamine and dibenamine were administered, then a subsequent administration of epinephrine failed to produce a rise in arterial potassium and also prevented the ventricular tachycardia and kept the blood pressure on a normal or constant state. They believe then that by some mechanism epinephrine under cyclopropane causes a liberation of potassium which in turn causes the cardiac arrhythmias.

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They believe now that cyclopropane anesthesia stimulates the

sympathetic system, producing a release of potassium from the liver, causing the heart, which is sensitized by cyclopropane, to develop a tachycardia and ventricular rhythm.

CARDIAC ARRHYTHMIAS IN MAN

Waters and Schmidt (341), Sise (301), and others (288) have called attention to the arrhythmia, bradycardia, and occasional rapid increase from a rate of 60 to 120 or more in man under cyclopropane anesthesia. Kurtz, Bennett, and Shapiro (175) in an electrocardiographic study on patients found ventricular extrasystoles in 55 per cent and multiple focus ventricular tachy-

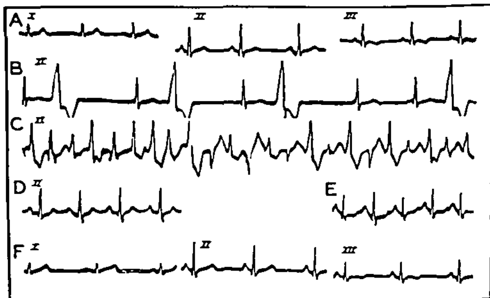


Fig 19 (Case 1) A woman, aged 23, with a normal heart had a laparotomy under cyclopropane There was nodal rhythm with frequent extrasystoles at thirty-seven minutes, second plane anesthesia during removal of appendix. Multiple focus ventricular tachycardia beginning one minute later, second and third planes of anesthesia, while the surgeon was exploring the pelvis. Return to normal rhythm at forty-three minutes A, before operation; B, in second plane of anesthesia at thirty-seven minutes, during removal of appendix; C, in second and third planes, from thirty-eight to forty-two minutes, during exploration of pelvis; D, in second plane at forty-three minutes, during removal of right tube; E, recovery at seventy-one minutes, F, eight hours after operation. (After Kurtz, Bennett, and Shapiro· J A M. A , 106, 434, 1936)

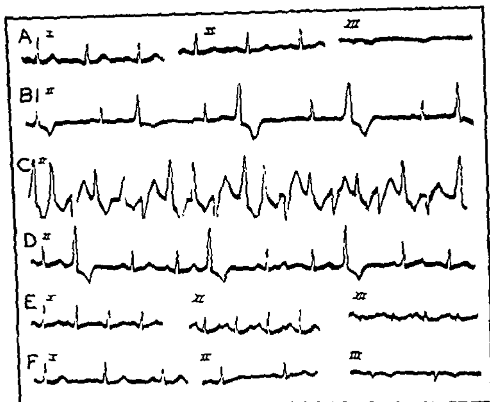


FIG 20 (Case 2) A woman, aged 32, with a normal heart had a pelvic operation under cyclopropane. There was ventricular extrasystolic rhythm at ten minutes during the preparation of the operative field, first plane anesthesia and multiple focus ventricular tachycardia at thirty-six minutes while the abdomen was being explored, first plane anesthesia Rhythm returned to normal before the end of the operation after passing through transition stage shown in D at forty-three minutes. A, before operation (leads I, II, and III); B, in first plane of anesthesia at ten minutes during preparation of field (lead II), C and D, first plane, thirty-six and forty-three minutes, respectively, exploration of abdomen (lead II), E, ten hours after operation (leads I, II, and III); F, five weeks after operation (leads I, II, and III) (After Kurtz, Bennett, and Shapiro. J A. M. A., 106, 434, 1936)

cardia in 10 per cent of the patients under cyclopropane anesthesia, records of two of their cases are shown in figures 19 and 20.

Thienes, Greeley, and Guedel (333) noted in their work that if one increased the concentration of cyclopropane above that necessary to produce respiratory arrest, the cardiac arrhythmic area might be passed through, and one would get into an area

sympathetic system, producing a release of potassium from the liver, causing the heart, which is sensitized by cyclopropane, to develop a tachycardia and ventricular rhythm.

CARDIAC ARRHYTHMIAS IN MAN

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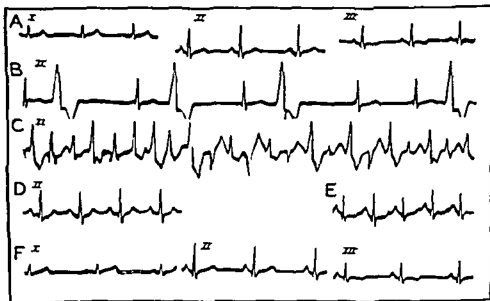


FIG 19 (Case 1) A woman, aged 23, with a normal heart had a laparotomy under cyclopropane There was nodal rhythm with frequent extrasystoles at thirty-seven minutes, second plane anesthesia during removal of appendix. Multiple focus ventricular tachycardia beginning one minute later, second and third planes of anesthesia, while the surgeon was exploring the pelvis. Return to normal rhythm at forty-three minutes A, before operation, B, in second plane of anesthesia at thirty-seven minutes, during removal of appendix; C, in second and third planes, from thirty-eight to forty two minutes, during exploration of pelvis; D, in second plane at forty-three minutes, during removal of right tube; E, recovery at seventy-one minutes, F, eight hours after operation (After Kurtz, Bennett, and Shapiro J. A M. A., 106, 434, 1936)

supplemental respiration was begun, and soon ventricular tachycardia was observed in twelve of fifteen patients. When the absorber was replaced in the system and supplemental respiration was given, normal rhythm returned in three to six minutes in all of the subjects, indicating at least that carbon dioxide excess had greater effect in producing cardiac arrhythmias of severe type than did oxygen lack.

Group 3—Hyperventilation and CO_2 accumulation in twenty-five patients. These subjects were carried in stage III, plane 1, surgical anesthesia with supplementation to the respiratory exchange with the carbon dioxide absorber out of the system for a period of twenty or thirty minutes. Ventricular extrasystoles and ventricular tachycardia were observed in six patients. The rhythm returned to normal in three to four minutes after the carbon dioxide absorber was placed in a line.

Group 4—Twenty-five patients that had major cardiac complications and major surgical procedures. In this group the subjects were maintained on supplemental respiration with adequate oxygen and adequate carbon dioxide absorption, and no arrhythmias were observed. He believes that the cardiac arrhythmias observed most frequently under cyclopropane anesthesia are a result of inadequate elimination of carbon dioxide and that these arrhythmias may be prevented providing supplemental respiration or controlled respiration is adequate.

Electrocardiographic records of his studies are shown in figures 21, 22, and 23.

In a subsequent study by Johnstone (159) on the effect of general anesthetics and cardiac inhibition, he observed arrhythmias present in sixty subjects and believed in part that arrhythmias were of the so-called vagal reflex type in which the action of the anesthetic upon the respiratory tract produced afferent impulses which in turn were sent down the vagus. He is of the opinion that this type of arrhythmia may be inhibited by using atropine in large doses, 1.2 mgm. or more.

with high cyclopropane in the inspired air in which cardiac arrhythmias would not be observed. Thus they have reported and have used 60 to 75 per cent cyclopropane in oxygen and reduced the frequency of cardiac arrhythmias. They believe that the cardiac arrhythmias are due to impulses arising in the hypothalamus, and that if the hypothalamus is depressed by this high concentration of cyclopropane, the impulses will not go down and cause arrhythmias of the heart. Likewise, Thienes and Greeley (332) have reported that the cardiac arrhythmias are most frequently observed at the level of respiratory arrest or apnea, and so they believe at the time they published their paper that in order to correct this an increase in the cyclopropane content with artificial respiration is the method of choice. This so-called arrhythmic area, at respiratory arrest, may be related to oxygen lack, carbon dioxide excess, or both, as noted below.

More recently, Johnstone (158) has published a study on cyclopropane anesthesia and ventricular arrhythmias in man. He studied the effect of cyclopropane, carbon dioxide excess, oxygen lack and artificial respiration in a series of ninety patients. These patients were divided into four groups.

Group 1—Hypoxia. Twenty-five patients were allowed to breathe on their own effort for five to fifteen minutes with deep cyclopropane anesthesia. Ventricular arrhythmias were observed in all twenty-five subjects and ventricular tachycardia in two and bigeminal rhythm in twenty-three. The rhythm in all patients returned to normal as soon as the respiration was supplemented by pressure upon the bag. This return to normal rhythm occurred in a period of two minutes or less following the supplemental respiration.

Group 2—Hypoxia and carbon dioxide excess. Fifteen patients were anesthetized to deep surgical anesthesia and diminished respiration caused a decrease in the oxygen intake and an increase in the carbon dioxide tension in the alveola. Cardiac irregularities and ventricular extrasystoles were observed in all patients. Then the carbon dioxide absorber was taken out of the system, and

supplemental respiration was begun, and soon ventricular tachycardia was observed in twelve of fifteen patients. When the absorber was replaced in the system and supplemental respiration was given, normal rhythm returned in three to six minutes in all of the subjects, indicating at least that carbon dioxide excess had greater effect in producing cardiac arrhythmias of severe type than did oxygen lack.

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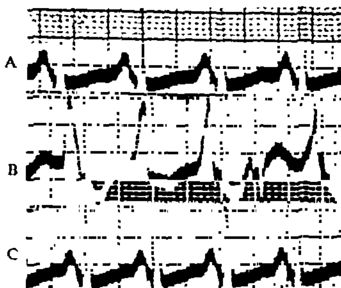


Fig. 21. All lead II

A After thirty minutes of cyclopropane anesthesia, with assisted respiration and CO_2 absorption

B. Spontaneous depressed respiration for the previous ten minutes with CO_2 absorption

C Assisted respiration resumed three minutes previously. (Johnstone Brit. Heart J., 12, 231, 1950)

RELATION OF PREMEDICATION TO THE CARDIAC IRREGULARITIES IN DOGS UNDER CYCLOPROPANE

While we were investigating the effect of premedication with morphine, barbital, and amytal upon the quantity of cyclopropane in the blood necessary for the different levels of anesthesia and respiratory arrest in dogs in which electrocardiographic records were made, it was observed in the dogs which received morphine before cyclopropane that bradycardia was the rule and that nodal rhythm and ventricular extrasystoles were routinely present during stage III_{1-4}, whereas in those receiving barbital or amytal the rhythm remained normal for as long as 20 to 40 minutes after respiratory arrest produced by cyclopropane. These observations led us to investigate the effect of cyclopropane and ether upon the heart after premedication with morphone.

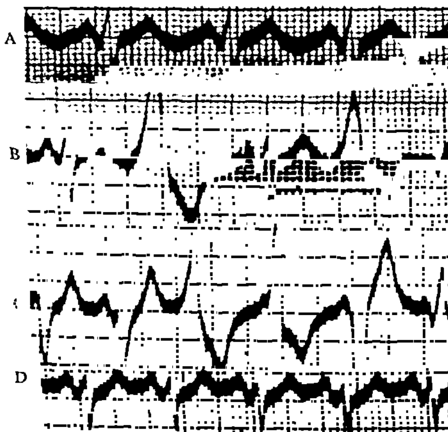


FIG 22. All lead II

A. After eleven minutes of cyclopropane anesthesia with assisted respiration and CO_2 absorption

B. Spontaneous depressed respiration for the previous five minutes, with CO_2 absorption

C Absorber turned off and assisted respiration resumed twenty minutes previously.

D Absorber inserted seven minutes previously. (Johnstone: Brit. Heart J , 12, 241, 1950)

MECHANISM OF ACTION OF ETHER AND CYCLOPROPANE IN ALTERING THE EFFECT OF MORPHINE ON THE PULSE

In a further study by Robbins, Fitzhugh, and Baxter (280) an attempt was made to determine the role of various components of the autonomic system in regulating the heart rate in dogs receiving morphine premedication and anesthetized with cyclo-

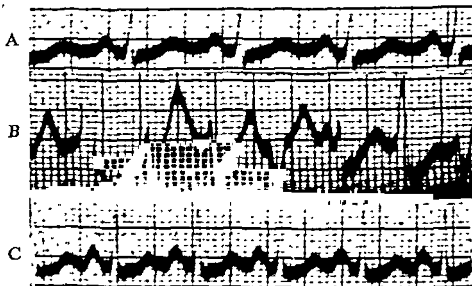


FIG 23. All lead II

A Before induction of anesthesia

B. After twelve minutes of cyclopropane anesthesia, with CO_2 accumulation Hyperventilating

C Absorber inserted five minutes previously. (Johnstone: Brit. Heart J., 12, 242, 1950)

propane and ether. The thoracic sympathetic chains (ganglia 1 to 5) were removed under aseptic technic, and two to three weeks later the adrenals were excised and vagi cut. A description of the procedure is given below.

Sympathetic Denervation of the Heart

The normal dog was placed on a dog board and control electrocardiograms and pulse-rate determinations were made. Bilateral thoracic sympathectomy was done under anesthesia and with aseptic technic. Anesthesia was induced by rebreathing in a bag containing cyclopropane in oxygen. After anesthesia was sufficiently deep to permit, a tracheal catheter with an inflatable cuff was inserted and then connected to a soda lime cannister and 6-liter bag containing cyclopropane in oxygen. The bag was emptied and refilled two or three times early in the procedure in order to remove inert gas. A second electrocardiogram was made

before the operation was started. The left side of the thoracic cavity was entered by an incision through the third intercostal space, beginning about two inches from the midsternal line and extending laterally for three inches; very few vessels were cut that required ligatures to stop the bleeding. After the thoracic cavity was entered, respiratory effort by the dog was abolished by over-ventilation, and this state was maintained throughout the operation, thus making it possible to select the time for artificial respiratory action when it would not interfere with the operative procedure. The lung was retracted to the midline and the thoracic sympathetic chain located and followed to the stellate ganglion, which was first dissected and cut from its anterior branches. The stellate ganglion was picked up with long forceps and held during the dissection of the thoracic trunk and ganglia down through the fifth or sixth ganglion. Usually the chain was taken out in one piece. Bleeding at the site of removal of the thoracic chain was so small as a rule that no special effort was necessary to stop it. The incision through the chest wall was closed in three layers; silk sutures were used. The right side of the thoracic cavity was entered immediately following the closure of the left, and the sympathetic ganglia and trunk removed. Closure was the same as for the left side except that immediately before the last suture in the pleural layer was tied, the lungs were inflated to their maximum and held in that state until the second layer of sutures was started; this procedure insures removal of air from both sides of the thoracic cavity in dog because of the functionally incomplete mediastinal septum. Sterile gauze dressing and adhesive were placed over the incision. A third electrocardiogram was made before the anesthetic was stopped.

Six out of eight dogs that survived the immediate operation recovered completely, although a fistula developed in one dog on the seventh postoperative day and closed on the tenth. The dogs were permitted to recover for fourteen to twenty-four days before further studies were made upon them.

The cardiosympathectomized dog was placed on the dog board

and a control electrocardiogram made from lead II, after which morphine sulfate (8 mgm. per kilogram) was given subcutaneously; thirty minutes later a second electrocardiogram was made. Surgical anesthesia was induced with cyclopropane in oxygen, and further electrocardiographic and pulse rate records were made. The anesthetic was discontinued and the dog permitted to return to the preanesthetic state, at which time electrocardiographic and pulse rate records were taken. Ether was then administered until surgical anesthesia was produced, when another electrocardiographic record was made. While under ether anesthesia, the abdomen was opened and the adrenal glands were dissected free of their surrounding tissue and excised after the vessels of the glands had been ligated. The abdomen was then closed and the anesthetic discontinued. Periods of forty to sixty minutes were allowed for the partial removal of ether, after which heart rate and electrocardiographic records were made.

Now, with the sympathetic fibers to the heart cut and the adrenals excised, cyclopropane and ether anesthesia were repeated as above. While the dog was under ether anesthesia the second time, the vagi were dissected and sectioned. The dogs were again permitted to return to the preanesthetic state, and further records were made. Cyclopropane and ether were again administered to the dogs after all autonomic pathways to the heart had been cut and the adrenals excised. The effects of administration of epinephrine intravenously and of stimulation of the vagi with weak tetanizing current upon the heart rate were determined. A second dose of morphine was given to each of four dogs after the autonomic fibers had been cut.

At the end of each experiment the dog was killed and the thoracic cavity opened to examine the lungs, as well as to see exactly how many ganglia had been removed. In all cases, at least the first five thoracic ganglia were removed. There was no fluid in the chest, and the lungs were in good condition.

The results of these experiments are shown in table 26; a complete protocol of one experiment is given in table 27.

TABLE 26*

Effect of ether and cyclopropane anesthesia upon the heart rate in dogs after section of the sympathetic and parasympathetic nerves to the heart

Condition of Dog	Experiment Number	Heart Rate			
		Control	Sympathetic to heart out	Sympathetic to heart and adrenals out	Sympathetic to heart, adrenals, and vagi out
Awake	24	120	90		
	25	160	130		
	27	140	140		
	28	125	115		
	30	65	88		
	31	90 (116)	100 (110)		
Morphine, 8 mgm. per kgm	24		58		
	25		65	87	155
	27		100	128	126
	28		84	66	76
	30		70	120	134
	31		62 (73)	98 (100)	165 (131)
Anesthetized with cyclopropane	24		62		
	25		39	55	155
	27		84	118	120
	28		66	58	74
	30		66	104	130
	31		58 (63)	90 (85)	160 (127)
Anesthetized with ether	24		100		
	25		125	130	160
	27		124	150	135
	28		128	82	78
	30		108	124	138
	31		92 (113)	135 (124)	168 (136)
Epinephrine, 0 06-0 01 mgm	25				160 → 250
	27				135 → 230
	28				72 → 165
	31				168 → 248
Vagus stimulated	25				160 → 15-60
	27				135 → 95
	31				168 → 98
Morphine, 6 mgm per kgm	25				160 → 155
	27				130 → 126
	28				78 → 72
	31				162 → 162

* Robbins, Fitzhugh, and Baxter: J Pharmacol and Exper. Therap , 66, 206, 1939 (280).

TABLE 27*

Experiment 25. Dog, 8 6 kgm , ♂. Thoracic sympathectomy, June 11, 1938. Experimental study, July 1, 1938 (8 4 kgm.)

Time	Procedure	Rate	Rhythm
8:30	Control	160	Sinus arrhythmia
9:00	Cyclopropane, III_3	120	Regular
9.00–10:30	Sympathectomy		
10.35	III_3	120	Regular
6/11–7/1	Recovery		
8.55	Control	130	Sinus arrhythmia
8.56	Morphine, 8 mgm. per kgm.		
9:34		60	Sinus arrhythmia marked
9:35	Cyclopropane on		
9:45	III_3	39	A-V dissociation
9:46	Cyclopropane off		
9:55	I	56	Sinus arrythmia marked
9:56	Ether on		
10:00	III_3	120	Sinus arrhythmia
10:20	Adrenals out		
10.21	Anesthetic off		
11·00	I	80	Sinus arrhythmia
11.02	Cyclopropane on		
11.10	III_3	55	Regular
11:11	Cyclopropane off		
11.30	I	92	Sinus arrhythmia
11:32	Ether on		
11·50	III_3	130	Regular
11 52	Vagi cut		
11 55		160	
11.56	Ether off		
1:00	I	160	
1:05	Morphine, 8 mgm per kgm.		
1 35	I	155	
1·47	Cyclopropane on		
2 05	III_3	155	
2.06	Cyclopropane off		
2.25	I	155	Regular
2.26	Ether on		
2.33	III_3	160	Regular
2:40	Vagal stimulation	15–60	A-V block
2:45	Epinephrine, 0 1 mgm	250	
2.50	Killed and autopsied Lungs clear Slight adhesions No fluid Sympathetic chain out in each side from 1–6 ganglia		

* Robbins, Fitzhugh, and Baxter. J. Pharmacol and Exper. Therap., 66, 206, 1939 (280)

The removal of the sympathetic innervation of the heart had little or no effect upon the rate. Morphine reduced the rate from 110 to 75, and anesthetization with cyclopropane further decreased the rate to 63, whereas anesthetization with ether increased the rate to 113. After the removal of the adrenals which, combined with surgical trauma, undoubtedly caused a fall in blood pressure, which reflexly produced a reduction of vagal tone through the carotid sinus mechanism, the heart rate remained at 100 after partial recovery from the ether. Subsequent anesthesia with cyclopropane caused a slowing of the pulse from 100 to 85, whereas ether anesthesia increased the rate to 124.

After vagal section, the heart rate increased to 131 in the awakened animal. Subsequent anesthesia with cyclopropane caused a reduction of heart rate of only 4 per minute, and ether anesthesia caused an increase of 5 per minute. The injection of epinephrine and vagal stimulation produced the expected rise and fall of the heart rate, respectively.

These results indicate that in the dog medicated with morphine the changes in the heart rate and rhythm brought about by cyclopropane anesthesia and by ether anesthesia are due to the action of these agents upon and through the vagal system (parasympathetic), and that the possible action of these agents upon the sympathetic system in relation to the heart rate is relatively small.

From the experiments discussed above, it seems that although cyclopropane produces an increase in heart rate in the normal dog, it decreases the heart rate in dogs after medication with morphine.

EFFECT OF PREMEDICATION UPON THE ELECTROCARDIOGRAPHIC AND BLOOD GAS CHANGES

With this evidence, then, that premedication with morphine before cyclopropane gave rise in the dog to the most frequent types of cardiac change in man (bradycardia, auriculoventricular block, nodal rhythm, and ventricular extrasystoles), we made further studies on the effect of premedication with morphine,

TABLE 27*

Experiment 25. Dog, 8 6 kgm., ♂ Thoracic sympathectomy, June 11, 1938
Experimental study, July 1, 1938 (8.4 kgm.)

Time	Procedure	Rate	Rhythm
8:30	Control	160	Sinus arrhythmia
9:00	Cyclopropane, III_3	120	Regular
9:00-10:30	Sympathectomy		
10:35	III_2	120	Regular
6/11-7/1	Recovery		
8:55	Control	130	Sinus arrhythmia
8:56	Morphine, 8 mgm. per kgm.		
9:34		60	Sinus arrhythmia marked
9:35	Cyclopropane on		
9:45	III_2	39	A-V dissociation
9:46	Cyclopropane off		
9:55	I	56	Sinus arrythmia marked
9:56	Ether on		
10:00	III_1	120	Sinus arrhythmia
10.20	Adrenals out		
10:21	Anesthetic off		
11:00	I	80	Sinus arrhythmia
11:02	Cyclopropane on		
11:10	III_2	55	Regular
11:11	Cyclopropane off		
11:30	I	92	Sinus arrhythmia
11:32	Ether on		
11:50	III_3	130	Regular
11:52	Vagi cut		
11.55		160	
11.56	Ether off		
1:00	I	160	
1 05	Morphine, 8 mgm per kgm.		
1.35	I	155	
1:47	Cyclopropane on		
2.05	III_2	155	
2:06	Cyclopropane off		
2:25	I	155	Regular
2:26	Ether on		
2:33	III_1	160	Regular
2:40	Vagal stimulation	15-60	A-V block
2:45	Epinephrine, 0 1 mgm.	250	
2:50	Killed and autopsied: Lungs clear; Slight adhesions; No fluid; Sympathetic chain out in each side from 1-6 ganglia		

* Robbins, Fitzhugh, and Baxter. J Pharmacol and Exper. Therap., 66, 206, 1939 (280)

cyclopropane was started and further samples taken and records made in stages III_{2-3}, III_4, and at respiratory arrest. In the dogs premedicated with barbital or amytal, blood samples and electrocardiographic records were made every five minutes after respiratory arrest until cardiac irregularities developed or until the heart stopped. Protocols of experiments in each group—morphine, barbital, and amytal—are shown in tables 28 to 31 with selected electrocardiographic records from each in figures 24 to 27.

A summary showing the blood gases and electrocardiographic studies on thirty-seven dogs is presented in table 32.

DISCUSSION

In the dogs receiving morphine, the heart rate fell from a control of 134 to 73; only one dog showed abnormal rhythm before

TABLE 29

Premedication on E.K.G. and gas changes. See also figure 25

Experiment 14

Time	Stage*	Arterial			E.K.G. Number	Heart Rate	P-R Interval	T Wave	Rhythm
		CO_2	O_2	C_3H_6					
		per cent	*per cent*	*mgm*			*seconds*		
9 10	Control				1	80	09–.12	+	Sinus arrhythmia
9 20	Barbital, 150 mgm per kgm								
9·45					2	155	08	+	Regular
10 20	III_3	14 8	19 1	8 2	3	210	08	–	Regular
10 59	IV	58 0	23 5	26 8	4	185	.07	+	Regular
11 04	IV	64 8	21 6		5	210	.08	–	Regular
11·09	IV	69 5	16 7		7	190	08	–	Regular
11 14	IV	72 0	8 45		9	170	08	–	Regular
11 17		74 8	2 35	26 8	10	120 0	09– 17	+	Slowing to arrest

* Stage III_3 = Absence of wink reflex and muscular relaxation; stage IV = Respiratory arrest

barbital, and amytal upon the electrocardiographic changes, oxygen, and carbon dioxide. These studies were essentially similar to those reported in tables 15 and 16. After the control samples of blood were taken and electrocardiographic records were made, the premedication was given, morphine subcutaneously or barbital and amytal intravenously; thirty minutes after the morphine and ten to twenty minutes after the barbital or amytal was given, second samples were taken for analysis and records made. The

TABLE 28*

The effect of morphine premedication upon blood gas and electrocardiographic changes during cyclopropane anesthesia See also figure 24

Experiment 19. Dog, 9 7 kilograms, male

Time	Stage	Arterial			E K G Number	Heart Rate	P R Interval	T Wave	Rhythm
		CO_2	O_2	C_3H_6					
		per cent	per cent	mgm					
1 10	Control	41 0	15 7		1	140	.1	+	Slight sinus arrhythmia
1·15	Morphine								
1.45		42 6	16 0		2	70	.1	+	Marked sinus arrhythmia
1.50	C_3H_6 on								
1 52					4	52	.12	+	Sinus arrhythmia; nodal extrasystoles
1:58	III_3				5	48	11		Nodal and ventricular extrasystoles
2:05	III_3	45 2	17.5	17 6	6	48	.11	+	Ventricular extrasystoles
2:15	III_{3-4}				7	50	.10– 12	+	Ventricular extrasystoles
2:25	III_4	46 8	16 1	23 4	8	46	.12	+	Ventricular extrasystoles
2:50	IV	57 2	16 2	27 0	12	62	12	+	Slight sinus arrhythmia
2:51	C_3H_6 off Recovery								

* Robbins, Baxter, and Fitzhugh Ann Surg , 110, 84, 1939 (279).

TABLE 31*

The effect of amytal premedication upon blood gas and electrocardiographic changes during cyclopropane anesthesia. See also figure 27

Experiment 13. Dog, 11 6 kilograms, female

Time	Stage	Arterial			E K G Number	Heart Rate	P-R Interval	T Wave	Rhythm
		CO_2	O_2	C_3H_6					
		per cent	*per cent*	*mgm.*			*seconds*		
8·55					1	150	.10	—	Sinus arrhythmia
9.00	Amytal, 30 mgm per kgm.								
9 20	I				2	140	.08	—	Regular
9.25	C_3H_6 on								
10:00	III_3	45.2	18.0	10.4	3	175	.07	—	Regular
11·00	IV	55.4	20.8	31.0	5	220	07	—	Regular
11·05	IV	63.5	18.95		6	250	.07	—	Regular
11:10	IV	66 5	15 7		8	210	.08	—	Regular
11·15	IV	67.8	8.4		10	175	.08	—	Regular
11 17 5		69.5	3.58	34.6	12	40-0	.10	—	Slowing to arrest

* Robbins, Baxter, and Fitzhugh. Ann. Surg , 110, 84, 1939 (279).

amytal is of the same order of magnitude as the concentration in the control dogs, so that the difference in the cardiac picture cannot be ascribed to a difference in the cyclopropane content.

There are three significant differences between the control group and the barbiturate-premedicated groups. First, cardiac irregularities or arrest developed in the control dogs on an average of six minutes after respiratory arrest, whereas in the barbital and amytal treated groups the cardiac arrest occurred about twenty minutes after respiratory arrest. Second, cardiac irregularities were recorded in seventeen of the nineteen control dogs (sixteen, nodal rhythm; five, auriculoventricular block; six, ventricular extrasystole), whereas in the fourteen dogs receiving barbiturates, irregularities were observed and recorded in only two dogs. This is particularly significant when one considers that in the group of

TABLE 30

The effect of amytal premedication upon blood gas and electrocardiographic changes during cyclopropane anesthesia. See also figure 26

Experiment 9

Time	Stage*	Arterial			E K G Number	Heart Rate	P-R Interval	T Wave	Rhythm
		CO_2	O_2	C_3H_6					
		per cent	*per cent*	*mgm*			*seconds*		
9:00	Control, Amytal, 30 mgm per kgm.				1	140	.10	–	Regular
9.20	I				2	170	.10	–	Regular
9.45	III_3	43.5	17 0	11.1	3	170	.10	–	Regular
10:40	IV	55 4	21.0	25 4	5	210	.09	–	Regular
10:45	IV	61 0	20 8		7	220	.09	–	Regular
10:50	IV	64.0	18 2		9	215	09	–	Regular
10:55	IV	67 5	13 0		11	195	.10	–	Regular
11 00	IV		6 5		16	165	.11	–	Regular
11.05	IV		3 8		21	150	11	–	Regular
11:10	IV		2 8	29.6	26	133	11	–	Regular
10:10 5	Heart stopped				27	60-0	13–.16	+	Rapid slowing to arrest

* Stage III_3 = Absence of wink reflex and muscular relaxation; stage IV = Respiratory arrest

cyclopropane. Anesthesia produced with cyclopropane reduced the rate to 54 per minute, and all dogs showed either nodal or ventricular extrasystoles, even though the arterial oxygen was 17.4 volumes per cent These results are markedly different from those obtained from dogs receiving cyclopropane alone and from dogs receiving barbiturates before the cyclopropane.

The records from the dogs receiving barbiturates show some things in common with the records of the non-premedicated control dogs. The arterial oxygen concentrations at which arrhythmias or arrest occurred are approximately the same in each group. The concentration of cyclopropane in the blood of the dogs receiving the smaller doses of barbital and in all those receiving

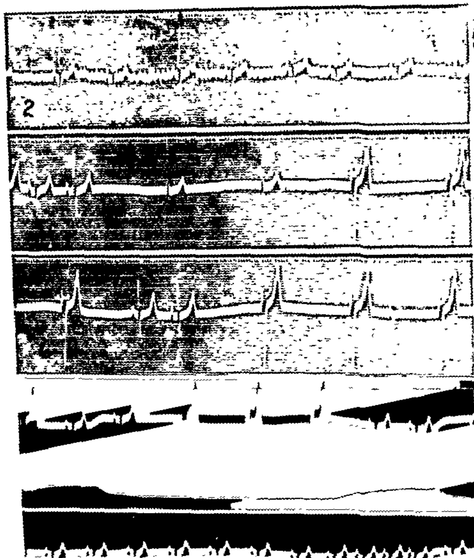


FIG 24 Electrocardiographic records from experiment 19, morphine, 5 mgm per kgm, was given as a preanesthetic drug

Consult table 28 for data which correlate the stage of anesthesia, arterial concentration of oxygen, carbon dioxide, and cyclopropane with the first three records in this figure

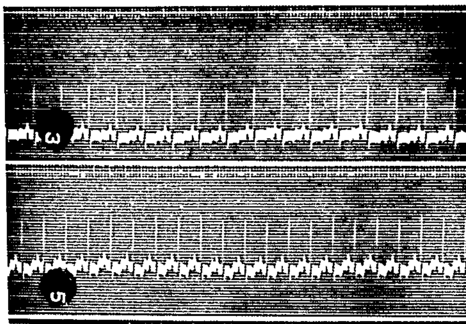
The irregularities of the heart in dogs under morphine-cyclopropane anesthesia are due to excessive vagal tone In records 16 and 18 the respiratory activity is correlated with the heart record The physiologic depression of the vagus center during inspiration permits the heart to beat normally, as shown in record 16 Two minutes after record 16 was made, the dog was given 10 mgm per kgm of amytal intravenously, three minutes later record 18 was made. This shows that amytal abolishes the excessive vagal tone. (Robbins, Baxter, and Fitzhugh. Ann Surg, 110, 84, 1939)

TABLE 32

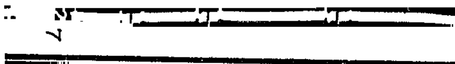
Cyclopropane anesthesia blood gas changes in normal and premedicated dogs

Number of Dogs	Premedication		Arterial Blood Gases										Time of Onset of Cardiac Irregularities or Arrest	Type of Cardiac Changes
	Type	Amount	Control		III_{2-4}			IV			Cardiac Irregularities or Arrest			
			O_2	CO_2	O_2	CO_2	C_3H_6	O_2	CO_2	C_3H_6	O_2	CO_2		
		mgm per kgm					*mgm*			*mgm*				
19			18 2	40 5	18 9	42 7	26 0	15 4	51 2	32 7	2.2	55.6	IV + 6.2 min.	Nodal rhythm—16 dogs A. V. block—6 dogs V. Ex.—5 dogs
6	Barbital	250*			17.7	52 0	15 6	20.6	59.2	24 6	3.6	70.0	IV + 20 min.	V. Ex.—1 dog Slowing to arrest—5
6	Amytal	30*			17 8	46.1	13.0	20.4	59 0	30.6	3 3	69 0	IV + 19 min	Slowing to arrest—6
6	Morphine	5	16 1	40.7	17 6	44.9	14.7	16.3	56.5	27.0	17 6	44.9	III_{2-4}	V. Ex.—5 dogs Nodal rhythm—4 dogs A. V. block—2 dogs

* The large doses of barbital and amytal reported in this table were used to see if one could prevent the development of cardiac irregularities which are observed in dogs after respiratory arrest, produced by cyclopropane, when the arterial oxygen content has been reduced to 3 to 4 volumes per cent. Severe anoxemia alone will cause irregularities of the type shown in figure 6.







27

FIG. 26. Electrocardiographic records from experiment 9 Amytal-Na was given as a preanesthetic drug See table 30 for further data on this experiment.

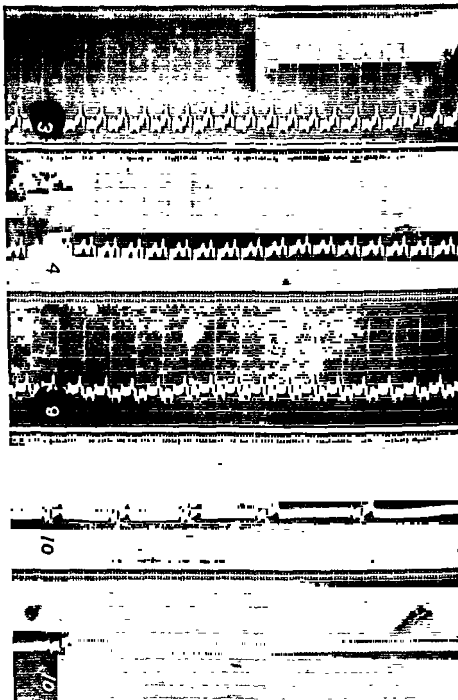


FIG 25 Electrocardiographic records from experiment 14. Barbital-Na was given as a preanesthetic drug See table 29 for data which correlate the stage of anesthesia, arterial concentration of oxygen, carbon dioxide and cyclopropane with these records

dogs receiving amytal, in which the cyclopropane concentration was equal to that in the controls, the final electrocardiographic records show normal complexes even up to cardiac arrest. Third, the arterial content of oxygen is increased at the time of respiratory arrest in the premedicated dogs. In the control group, the oxygen content in surgical anesthesia was 18.95 volumes per cent and at respiratory arrest was 15.40 volumes per cent, whereas in the amytal group the values were 17.8 and 20.4 volumes per cent, respectively, and in the barbital group the concentration at respiratory arrest was 20.5 volumes per cent. In three dogs receiving barbiturate-premedication the oxygen capacity of the arterial blood in surgical anesthesia and at respiratory arrest was found to be 17.8 volumes per cent and 19.9 volumes per cent, respectively.

Dogs anesthetized with cyclopropane to the stage of respiratory arrest are easily revived by discontinuing the anesthetic and giving artificial respiration for a few seconds. In a group of dogs which received barbiturate premedication and were forced to respiratory arrest with cyclopropane, several were revived five to thirty-five minutes after respiratory arrest.

STUDIES ON THE PREVENTION OF CARDIAC ARRHYTHMIAS PRODUCED BY EPINEPHRINE DURING CYCLOPROPANE ANESTHESIA

Several studies have been made in the laboratory to determine the effect of drugs in preventing or abolishing the cardiac arrhythmias observed under cyclopropane anesthesia and particularly those arrhythmias that are produced by the administration of epinephrine during cyclopropane anesthesia. As noted above, we (279) have reported studies upon the effect of barbiturate premedication in the prevention of the cardiac arrhythmias that are ordinarily observed at the time of or soon after respiratory arrest in the dog. These studies have been reinvestigated by Orth and his associates, and these authors have published papers showing the failure of various barbiturates to prevent the cyclopropane-epinephrine arrhythmias in dogs, and failure also to prevent the spontaneous arrhythmias that occur in dogs that are given arti-

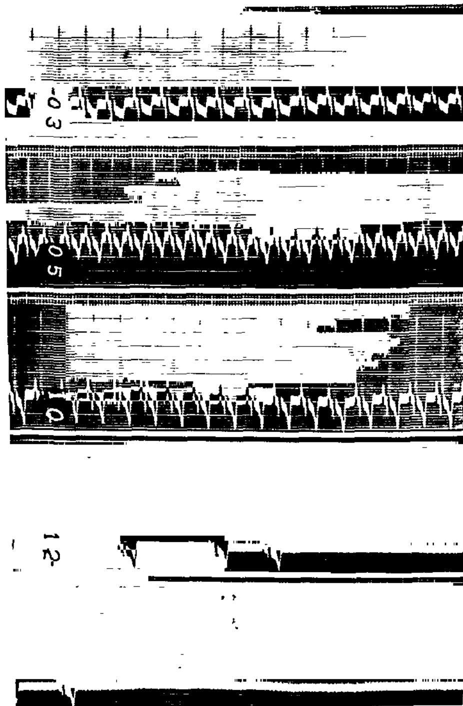


FIG 27 Electrocardiographic records from experiment 13. Amytal-Na was given as a preanesthetic drug See table 31 for further data on this experiment (Robbins, Baxter, and Fitzhugh Ann Surg, 110, 84, 1939)

ether anesthesia for fifteen minutes and then changed to cyclopropane, 22 volumes per cent, for a period of thirty minutes. At the end of this time epinephrine was administered intravenously, and in sixteen of the twenty-one dogs there was protection against the tachycardia and only five had any arrhythmias and these were for an average period of forty-five seconds. There were no data in this paper as to concentration of ether in the blood at the time the epinephrine was given during the inhalation of the twenty-two per cent mixture of cyclopropane, but on previous studies in many places it has been shown that the excretion of ether is relatively slow and that approximately half of the blood concentration persists for at least thirty to sixty minutes following the cessation of this administration.

More recently Greisheimer and her associates (121) have published a study on the effect of ether on the cyclopropane-epinephrine arrhythimas. In dogs where the blood concentration of ether was 58 mgm. per 100 cc., approximately one-half of the full surgical anesthetic dose, and 11 mgm. of cyclopropane per 100 cc., again a little over one-half of the full anesthetic dose, thirteen of eighteen animals were protected against the epinephrine arrhythmias when they were on the combined anesthetic mixture of ether and cyclopropane. They made simultaneous determinations of carbon dioxide and oxygen, and these agents were found to be in normal concentration.

Another study upon the effect of sympathomimetic amines on cardiac arrhythmias during cyclopropane anesthesia and during ether anesthesia in dogs has been published by Deterling and his associates (84). In fourteen experiments, the intravenous administration of .3 to .9 micrograms of norepinephrine per kilo in dogs under cyclopropane anesthesia produced premature ventricular contractions in twelve animals and ventricular tachycardia in two, whereas in twenty-three experiments under ether anesthesia this drug produced no cardiac arrhythmias. In twelve experiments with epinephrine .3 to .9 micrograms per kilo, in dogs under cyclopropane anesthesia, premature ventricular contractions were observed

ficial respiration with a mixture of cyclopropane that may vary from one to two times that necessary to produce respiratory arrest.

Barbiturates. In the paper by Lee and his associates (181), the dogs were given 10 mgm. of amytal sodium per kilo and then administered cyclopropane in concentrations of sixty per cent. In an experiment of this design, there was no protection of the dog heart by the administration of the amytal. Orth and his associates (247), in using thiopental sodium, seconal, pentobarbital sodium, amytal sodium, sodium barbital and delvinal in animals, have failed to observe any protection against cardiac arrhythmias when these animals were given the standard dose of epinephrine during surgical anesthesia produced by cyclopropane. Neither of these sets of studies produces evidence that barbiturate premedication in the human subject or in the dog would not prevent the normal spontaneously occurring arrhythmias that one frequently sees in deep surgical anesthesia and at the time of respiratory arrest.

Ether. Early observations by Meek and his associates (210), in 1937, showed that under cyclopropane anesthesia cardiac arrhythmias were frequently and almost routinely observed after the injection of epinephrine, and that also they were frequently observed when epinephrine was injected during chloroform anesthesia. They noted that when the standard dose of epinephrine was injected under either light or deep ether anesthesia, cardiac arrhythmias of the ventricular type were totally absent. They were the first to show that the cardiac arrhythmias with epineprhine and cyclopropane could be prevented by the simultaneous administration of diethyl ether. Milowsky and Rovenstine (213) used ether to abolish arrhythmias.

In 1942, Stutzman and his associates (317) made an extensive study on the prevention of cyclopropane-epinephrine tachycardia by diethyl ether In twenty-one dogs under cyclopropane anesthesia, the administration of epinephrine produced ventricular tachycardia of an average of forty-two seconds' duration in all of the twenty-one dogs. Twenty-one dogs were placed under deep

In a subsequent study by Stutzman and his associates (318) on twenty-seven dogs in which fibrillation had been produced during cyclopropane anesthesia by the injection of epinephrine, they were unable to restore any dog to normal cardiac function as a result of the injection of 16 mgm. per kilo of procaine within thirty sseconds after the fibrillation developed. They felt from their studies that procaine had no beneficial effect whatsoever upon the altered cardiac mechanism as a result of cyclopropane and epinephrine simultaneously.

Smith and Ferguson (302) in 1949 reported the results of their studies on the use of procaine hydrochloride upon the cardiac arrhythmias resulting from the intravenous administration of epinephrine in dogs during cyclopropane anesthesia. Like Stutzman and his associates, Smith and Ferguson obtained no protective effect with the use of procaine. They did, however, feel that procaine might correct arrhythmias which were due to excessive vagal stimulation.

Procaine amide. Morris and his associate (220) studied the effect of procaine amide on the cardiac irregularities during anesthesia in twenty-five experiments on thirteen dogs. They used doses of 10 to 60 mgm. per kilo of procaine amide, and in eight of these thirteen dogs that had had the most careful study before the anesthesia, it was found that after they had had the procaine amide and their standard dose of epinephrine injected intravenously, ventricular tachycardia was observed in seven and ventricular fibrillation was noted in two, so they feel that there is no protection whatsoever with procaine amide against the cardiac arrhythmias produced in dogs.

Regitine. Morris and his associates (222) have reported on the laboratory and clinical observation on the effect of regitine on cardiac irregularities during cyclopropane anesthesia. They found in dogs with ventricular tachycardia that there was a reversion to sino-auricular tachycardia in four out of five. When this drug was tried in man, however, there was no alteration in the arrhythmias observed, so it is felt that regitine is of no benefit in treating the cardiac irregularities in man during cyclopropane anesthesia

in three, ventricular tachycardia in one, and no arrhythmias in seven. In the dogs under ether anesthesia epinephrine produced no cardiac arrhythmias. With phenylephrine .3 to .6 micrograms in three animals under cyclopropane, no arrhythmias were observed nor were any observed in animals under ether. They conclude that with ether anesthesia these three sympathomimetic amines do not give rise to any cardiac arrhythmias, whereas with cyclopropane anesthesia only phenylephrine did not produce arrhythmias.

In a general discussion on the effect of drugs in the prevention of cardiac irregularities during anesthesia, Orth (242) states that three conditions are necessary for the production of these irregularities· (1) cyclopropane must reach the heart directly, (2) the brain centers above the pons must be intact, and (3) sympathetic fibers to the heart must be intact.

Bennett, Dhuner, and Orth (20) found in the dog and the monkey at least that dihydroergocornine in doses of .2 mgm. per kilo was the best agent to give protection against the cyclopropane-epinephrine cardiac irregularities. As a result of their studies on the dog and on monkeys, they tried this drug in the protection of cardiac irregularities in twenty-three patients and found that it had no value.

Procaine. The effect of procaine and similar chemical substances upon the frequency or the prevention of cardiac arrhythmias in the experimental animal under cyclopropane and the prevention of arrhythmias in the human subject in clinical anesthesia has been investigated by several groups (9).

Burstein and his associates (54, 55) have reported upon the protective action of procaine against ventricular fibrillation induced by epinephrine during cyclopropane anesthesia. In addition to procaine they studied the effects of para-aminobenzoic acid itself and sodium para-amino benzoate. The drug was given before the epinephrine, and in three animals they gave procaine during the period of what was interpreted to be, by the electrocardiogram, ventricular fibrillation in dogs In two of these three dogs the normal rhythm eventually ensued.

In a subsequent study by Stutzman and his associates (318) on twenty-seven dogs in which fibrillation had been produced during cyclopropane anesthesia by the injection of epinephrine, they were unable to restore any dog to normal cardiac function as a result of the injection of 16 mgm. per kilo of procaine within thirty sseconds after the fibrillation developed. They felt from their studies that procaine had no beneficial effect whatsoever upon the altered cardiac mechanism as a result of cyclopropane and epinephrine simultaneously.

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Quinidine. Huggins and his associates (153) have reported on the study on the effect of quinidine on arrhythmias induced by cyclopropane and epinephrine. By the administration of 1 to 5 mgm. of quinidine per kilo, they observed protection against cardiac irregularities resulting from the injection of epinephrine for a period of twenty-four to twenty-five minutes. A dose of 20 mgm. per kilo protected against the arrhythmias for one to three hours.

Dibenamine. Nickerson and his associates have reported in several papers their studies upon the effect of dibenamine in the prevention of cardiac arrhythmias produced in the experimental animal during cyclopropane anesthesia by the intravenous injection of epinephrine and also the use of this agent against the spontaneous arrhythmias that occur during cyclopropane anesthesia in the human subject. In 1946, Nickerson, Smith, and Goodman (235) made their first report on the use of this drug in the prevention of cardiac arrhythmias in dogs. In a series of fourteen control dogs in which the fixed dose of epinephrine was injected during cyclopropane anesthesia, eight died as a result of ventricular fibrillation. The duration of irregularities was one hundred thirty-seven seconds, and the duration of ventricular tachycardia was ninety-seven seconds. In the dogs that were given dibenamine before the epinephrine was given, there were no deaths as a result of ventricular fibrillation, there was no incidence of ventricular tachycardia, and the average duration of cardiac arrhythmias was only four seconds (232). However, the dogs that were treated with dibenamine did show marked sinus tachycardia. In a later study, Nickerson and Smith (234) observed the effects of procaine, meperidine, and dibenamine on the cardiac irregularities produced by cyclopropane and epinephrine. They observed some protection against ventricular extrasystoles and ventricular tachycardias with procaine but no protective effect against ventricular fibrillation. With meperidine there was a reduction in the duration of ventricular tachycardia. With dibenamine 20 mgm. per kilo intravenously, thirty minutes before the epinephrine, pro-

tection against ventricular tachycardia was 100 per cent, and in only five of twenty-eight dogs were ventricular extrasystoles observed following the administration of the epinephrine. They believe that dibenamine would be a satisfactory agent to use to prevent the cardiac arrhythmias in patients.

Nickerson and Nomaguchi (233) in their experimental study on the mechanism of the action of dibenamine conclude two points. First, that there is a direct depression of the cardiac muscle with a large dose of dibenamine. Second, that dibenamine prevents the rise in blood pressure as a result of the epinephrine injection and this in turn protects against the cardiac arrhythmias that are ordinarily observed.

Moe and his associates (214) have reported upon the mechanism by which dibenamine might produce the protection against the cardiac arrhythmias. They feel that a major factor in the production of arrhythmias is the hypertension that ensues immediately following the administration of epinephrine. They observed in the preliminary studies that 20 mgm. per kilo of dibenamine prevented the arrhythmias that followed the injection of epinephrine during cyclopropane anesthesia and attributed it to the fact that it prevented the increase in blood pressure as a result of epinephrine. They found in this study that if the aorta was clamped so that the blood pressure was increased from 50 to 100 mm. of mercury, then epinephrine will cause the arrhythmia. They felt that the direct accelerator action of epinephrine and the increased blood pressure resulting from epinephrine were necessary to set off the system giving rise to ventricular arrhythmias.

In 1948, Moe and his associates (215) published a paper on the role of arterial pressure in the induction of idioventricular rhythms under anesthesia. They conclude from their study that dibenamine reverses the pressor action of epinephrine in dogs and protects them against the induction of idioventricular rhythms under cyclopropane. Also the idioventricular rhythms, but not ventricular fibrillation, can still be induced by epinephrine after dibenamine if the arterial pressure is mechanically elevated. They

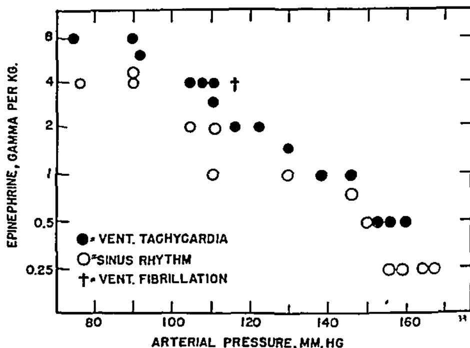


FIG. 28. Experiment 10-21-47 Dog 8 kgm. Cyclopropane-oxygen Pressure regulator in abdominal aorta Relation between dose of epinephrine and arterial pressure necessary to produce ventricular tachycardia (Moe *et al.*: J. Pharmacol & Exper Therap, 94, 319, 1948)

also observed that there was a quantitative relationship between the level of arterial pressure and the threshold dose of epinephrine required to produce ventricular arrhythmias as shown in figure 28.

McMillan and his associates (207) used another technic in an effort to study the effect of dibenamine upon the prevention of the arrhythmias as the result of epinephrine under cyclopropane. They placed their dogs on the constant concentration of sixteen per cent cyclopropane with adequate respiratory exchange and determined the amount of epinephrine that was necessary to produce arrhythmias when there was a constant flow over a period of considerable time. In the control animals, the arrhythmias or extrasystoles developed after .7 to 1.8 micrograms of epinephrine per kilo had been injected. After the preliminary treatment with dibenamine, 20 mgm. per kilo, it was necessary to inject at a con-

stant rate somewhere between 89 and 300 micrograms of epinephrine per kilo. Thus the total dose needed after dibenamine to produce cardiac arrhythmias varied from 100 to 200 times that necessary before the dibenamine was administered.

Murphy and his associates (225), in a study on the effect of the alteration in blood pressure upon the ventricular tachycardia resulting from the injection of epinephrine during cyclopropane anesthesia, found that a rise in pressure was not an essential factor in the production of the tachycardia, for in twelve experiments when the blood pressure rise was held from 2 to 25 mm. of mercury above the control, ventricular tachycardia was routine and of about as long duration as when the blood pressure was permitted to rise from 32 to 100 mm. of mercury, so they believe that there is no relation between the blood pressure changes and the cardiac arrhythmias.

Fawaz (97) used the heart-lung preparation of the dog in an effort to determine the possible site of the action of dibenamine in protecting the heart against arrhythmias upon the injection of various sympathomimetic amines when cyclopropane was being administered to the lung. Dibenamine did not protect against the cyclopropane-epinephrine arrhythmias in this experimental setup, so he believes the site of action of dibenamine in protecting against it in the intact animals must lie in a region other than the heart-lung system.

Thoracic sympathectomy and tetraethyl ammonium. Rennick and his associates (265) have studied the effect of thoracic sympathectomy in dogs upon the induction of ventricular rhythm by epinephrine and cyclopropane and also in dogs that have had their sympathetic pathways blocked by tetraethyl ammonium. They observed after sympathectomy or after tetraethyl ammonium that the threshold dose of epinephrine had to be increased and that a given dose of epinephrine did not produce the rise in blood pressure as it did before. They found that if the blood pressure rise was the same as in the control, there was no protection against the cyclopropane-epinephrine arrhythmias. They feel that the

possible beneficial effects that Stutzman and Pettinga (321) obtained by evisceration were due in part to the fall in systemic blood pressure as a result of the evisceration and that this fall in blood pressure gave some protection against the standard dose of epinephrine.

STUDIES ON THE PREVENTION OF CARDIAC ARRHYTHMIAS IN MAN

Procaine amide. In a study on patients by Morris and Haid (220), forty-three women undergoing gynecological procedures were investigated for the beneficial effects of procaine amide. Nineteen patients served as a control without the benefit of the procaine amide, and in twenty-four procaine amide was given in amounts of 1 gram before the anesthetic was started, and in some of the twenty-four it was given intravenously during anesthesia, but the dose when given by both routes never exceeded 2 grams. They observed irregularities in 23 of the twenty-four cases, with premature ventricular contraction in fourteen and ventricular tachycardia in fourteen patients that received procaine amide. Only one of the twenty-four treated patients remained free of arrhythmias. The frequency of irregularities in patients receiving procaine amide was similar to that of the control group. In two patients in which ventricular fibrillation resulted on the table, the intracardiac injection of .5 grams of procaine amide during the cardiac arrest failed to restore any satisfactory cardiac function. Thus Morris and Haid feel that there is no protective effect on the cardiac irregularities produced by cyclopropane by the intravenous injection or oral treatment of the subject with procaine amide.

Peters and his associates (254) have reported on the effect of the intravenous administration of procaine amide upon the cardiac arrhythmias observed during intubation under cyclopropane or cyclopropane-ether anesthesia. Their technic was to administer 300 mgm. of procaine amide intravenously before the anesthetic was started, and then they induced anesthesia with cyclopropane in fifty-one patients, and a mixture of cyclopropane-ether in the

forty-nine patients; when plane 2 or 3 of surgical anesthesia had been reached, intubation was carried out. In those subjects that had procaine amide as preanesthetic medication, seventeen per cent showed cardiac arrhythmias during the period of intubation, whereas in those that were studied in another series, one hundred and three patients, without procaine amide sixty per cent showed cardiac arrhythmias during the period of intubation. They feel that there was a protection against the cardiac arrhythmias as a result of administration of this drug but that hypoxia, too light a level of anesthesia, and repeated attempts at intubation caused reflex arrhythmias during cyclopropane anesthesia.

Secobarbital. We (270) have studied a series of patients recently in which intubation was carried out under cyclopropane anesthesia after premedication with barbiturates and atropine, or after premedication with morphine and atropine. The frequency of arrhythmias before intubation was 16 per cent in the barbiturate-atropine group and 25 per cent in the morphine-atropine group. After intubation, 25 per cent of the barbiturate-atropine group and 55 per cent of the morphine-atropine group showed some type of cardiac arrhythmia. In a total of sixteen patients that were given 1 mgm. of secobarbital per kilo intravenously, normal rhythm returned within twenty to forty seconds after the injection was completed. Electrocardiographic records of two patients are shown in figure 29A and figure 29B. See Chapter 8 page 194 for a complete discussion of these studies.

Dibenamine. Nickerson and Brown (231) have made a careful study upon the effect of dibenamine and the cardiac arrhythmias in patients, with the continuous observation of electrocardiographic changes for several minutes before the anesthesia was started and during the complete period of anesthesia. They also made studies upon the effect of the depth of anesthesia in relation to the frequency and type of arrhythmias that were observed. These observations are shown in table 33. Their studies included results on seven patients without dibenamine premedication, seven patients that had received 5 to 6 mgm. per kilogram of di-

possible beneficial effects that Stutzman and Pettinga (321) obtained by evisceration were due in part to the fall in systemic blood pressure as a result of the evisceration and that this fall in blood pressure gave some protection against the standard dose of epinephrine.

STUDIES ON THE PREVENTION OF CARDIAC ARRHYTHMIAS IN MAN

Procaine amide. In a study on patients by Morris and Haid (220), forty-three women undergoing gynecological procedures were investigated for the beneficial effects of procaine amide. Nineteen patients served as a control without the benefit of the procaine amide, and in twenty-four procaine amide was given in amounts of 1 gram before the anesthetic was started, and in some of the twenty-four it was given intravenously during anesthesia, but the dose when given by both routes never exceeded 2 grams. They observed irregularities in 23 of the twenty-four cases, with premature ventricular contraction in fourteen and ventricular tachycardia in fourteen patients that received procaine amide. Only one of the twenty-four treated patients remained free of arrhythmias. The frequency of irregularities in patients receiving procaine amide was similar to that of the control group. In two patients in which ventricular fibrillation resulted on the table, the intracardiac injection of .5 grams of procaine amide during the cardiac arrest failed to restore any satisfactory cardiac function. Thus Morris and Haid feel that there is no protective effect on the cardiac irregularities produced by cyclopropane by the intravenous injection or oral treatment of the subject with procaine amide.

Peters and his associates (254) have reported on the effect of the intravenous administration of procaine amide upon the cardiac arrhythmias observed during intubation under cyclopropane or cyclopropane-ether anesthesia. Their technic was to administer 300 mgm. of procaine amide intravenously before the anesthetic was started, and then they induced anesthesia with cyclopropane in fifty-one patients, and a mixture of cyclopropane-ether in the

forty-nine patients; when plane 2 or 3 of surgical anesthesia had been reached, intubation was carried out. In those subjects that had procaine amide as preanesthetic medication, seventeen per cent showed cardiac arrhythmias during the period of intubation, whereas in those that were studied in another series, one hundred and three patients, without procaine amide sixty per cent showed cardiac arrhythmias during the period of intubation. They feel that there was a protection against the cardiac arrhythmias as a result of administration of this drug but that hypoxia, too light a level of anesthesia, and repeated attempts at intubation caused reflex arrhythmias during cyclopropane anesthesia.

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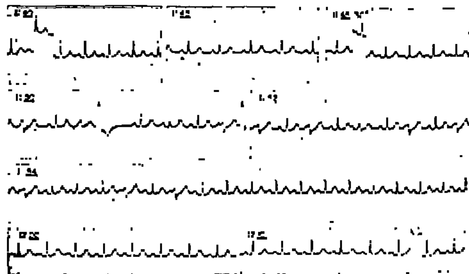


FIG 29A Electrocardiographic records from patient E., female, age 50, weight 150 pounds. Operation removal of solitary tumor of thyroid Soluble phenobarbital 0 13 gram at 10 00 A M.; atropine .0004 at 10:45 A M. Control EKG at 11:40 A.M Cyclopropane-oxygen at 11:41 A M. Endotracheal intubation between 11:45 and 11 45 20" 11 50 to 11:54 abnormal ventricular complexes from various foci At 11.53 30", seconal, 75 mgm. was given intravenously. Record 11:54 shows the transition from abnormal to normal rhythm which persisted throughout the rest of the anesthesia

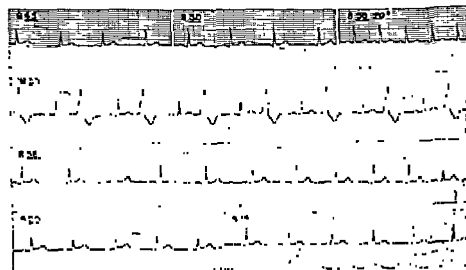


FIG 29B Electrocardiographic records from patient P C., male, age 34, weight 160 pounds Operation removal of solitary tumor of thyroid. Morphine .01 gram at 6:30 A.M. and atropine 0004 at 7 30 A M Control EKG at 8:45 A M Cyclopropane-oxygen at 8 46 A M Endotracheal intubation between 8:50 A M. and 8:50 20" A M. Single focus ventricular extrasystoles at 8:52 to 8:55 at which time seconal, 75 mgm., was given intravenously. At 8 56 the rhythm had returned to normal and remained so throughout the rest of the anesthesia.

TABLE 33*

Cardiac arrhythmias exhibited by patients in various planes and stages of cyclopropane anesthesia

Treatment	Depth of Anesthesia	Total Time	Sinus Rhythm	Nodal or Auricular Rhythm	Ventricular Beats 1/3	Ventricular Beats 1/3	Ventricular Tachycardia
		min	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Control (7 cases)	III_1	12	96	4			
	III_2	31	82	18			
	III_3	57	53	34	5	8	
	III_4	62	50	24	10	13	3
	IV	30	33	24	17	13	13
Dibenamine, 5.0 to 6.0 mgm. per kilogram (7 cases)	III_1	19	100				
	III_2	28	96	2	2		
	III_3	57	85		4	11	
	III_4	67	65	9	12	13	1
Dibenamine, 7.0 to 7.5 mgm per kilogram (6 cases)	III_1	14	100				
	III_2	29	95	5			
	III_3	46	91	9			
	III_4	36	94	3	3		
	IV	23	90		10		

* After Nickerson and Brown Anesthesiology, 12, 216, 1951 (231).
See figure 30 for other analysis of these data.

benamine, and six patients that had received 7 to 7.5 mgm. per kilo of dibenamine intravenously. The dibenamine was given by infusion over a period averaging thirty-eight minutes. This infusion was given anywhere from seventeen minutes to fourteen hours before the anesthetic was started. The duration of effect of dibenamine extended from thirty minutes to eighteen hours following a single intravenous administration. Figure 30 taken from their paper is a summary of the investigation. By making a continuous recording of the cardiac pattern on the electrocardiograph, they were able to determine very carefully the type of arrhythmias and the duration of their presence, and they have classified the cardiac patterns observed into four groups. One, nodal or auricular rhythm; two, ventricular beats amounting to less than a third of the total number of beats, three, ventricular beats amounting to

more than a third of the total number of beats including pulsus bigeminus; and four, ventricular tachycardia. These four categories were assigned arbitrary values of one, three, five, and ten, respectively, as a measure of the relative severity of each arrhythmia. The severity of the arrhythmias was then plotted against the depth of anesthesia and these values are shown in figure 29. It is observed that in the control non-medicated patient, the index of arrhythmias is much higher than in the other two groups and that when dibenamine has been given in 7 to 7.5 mgm. per kilogram, the index of arrhythmias is less than .2. It can also be noted as the depth of anesthesia is increased, the index of arrhythmias is increased. In the three groups of patients observed, the pressure changes were approximately the same throughout, that is the patients receiving dibenamine did not have a more marked fall in

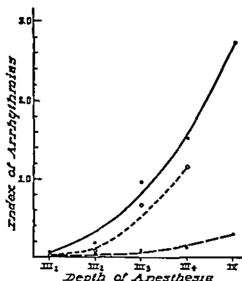


FIG 30 Relation of cardiac arrhythmias to depth of cyclopropane anesthesia in control patients and in patients premedicated with various doses of dibenamine. ●——● Controls O- - -O Treated preoperatively with 5 0 to 6 0 mgm. per kilogram of dibenamine ●— — ● Treated preoperatively with 7.0 to 7.5 mgm per kilogram of dibenamine See table 33 (Nickerson and Brown· Anesthesiology, 12, 216, 1951)

TABLE 31*

Blood pressures during operation, averaged by groups

Groups	Maximum		Minimum	
	Systolic/diastolic	Pulse pressure	Systolic/diastolic	Pulse pressure
Control (7 cases)	143/85	58	96/56	40
Dibenamine, 5.0 to 6.0 mgm. per kilogram (7 cases)	143/70	73	116/62	54
Dibenamine, 7.0 to 7.5 mgm per kilogram (6 cases)	143/76	67	107/51	56

* After Nickerson and Brown. Anesthesiology, 12, 216, 1951 (231).

blood pressure than did those not receiving dibenamine as recorded in table 34.

Nickerson and Brown (231) concluded that the effect of dibenamine is not upon the alteration in the blood pressure but is due to a direct action of the substance in producing a blockade of adrenergic stimuli to the myocardium itself.

CARDIAC OUTPUT STUDIES DURING CYCLOPROPANE ANESTHESIA

Dog. We (276) have determined the cardiac output under different levels of anesthesia produced by cyclopropane in trained dogs. The cyclopropane content of the blood at the different stages of anesthesia and at respiratory arrest has been determined. Electrocardiographic records were made during each determination of the cardiac output.

Methods Used

Calculation of the cardiac output. The Fick principle for calculating the output was used.

Cardiac output

$$= \frac{\text{cc. of oxygen consumed per minute}}{\text{arterial oxygen (per cent)} - \text{venous oxygen (per cent)}} \times 100$$

Blood gas analysis. The blood was collected in 10 cc. syringes under 4 cc. of mineral oil in which dry powdered sodium oxalate was suspended and in which four or five BB shot were placed to facilitate mixing the sample at the time of analysis. The arterial samples were taken from the right femoral artery and the venous sample from the right ventricle by needle puncture. As soon as the samples were collected, they were placed in an ice box until analyzed. One cubic centimeter samples of blood were analyzed in a Van Slyke-Neill apparatus according to the procedure given by Peters and Van Slyke (253). Duplicate analyses were made as a rule. Studies by Orcutt and Waters (240) have shown that the presence of cyclopropane in the samples taken under anesthesia does not alter the accuracy of the oxygen and carbon dioxide determinations.

Cyclopropane in the blood and the gas mixture was determined by the iodine pentoxide oxidation method.

Oxygen consumption. Oxygen consumption was determined by use of a Sanborn Graphic Metabolism Tester. The volume of oxygen used was corrected for the temperature and pressure observed.

Method of anesthesia. After the normal metabolic period had been conpleted, the dog was made to rebreathe a cyclopropane-oxygen mixture from a 6-liter bag until anesthetized, after which a tracheal catheter with an inflatable cuff, Guedel-Waters (134), was inserted, and then the catheter was connected to the Sanborn Graphic apparatus wich had been filled with an oxygen mixture containing 15 to 25 per cent cyclopropane. Oxygen was admitted at the rate of consumption, and the cyclopropane concentration either increased or decreased until the dog was in the desired level of anesthesia, in which he was kept for at least fifteen minutes. The flow of oxygen into the spirometer was then discontinued and the output determination made. Because of the rapid rate of elimination of cyclopropane after its administration is stopped, it was necessary to keep the animal breathing a cyclopropane mixture during the test period. In order to make the proper corrections

for the cyclopropane absorbed or blown off by the dog during the test period, the concentration of cyclopropane present in the spirometer at the beginning and at the end of the period was determined. As a rule, the change in the concentration of cyclopropane during the test period was no greater than the experimental error of the method used, so that the only correction necessary was for the amount of cyclopropane absorbed from the volume of oxygen used. In a few instances, however, the change was greater than the error of the method, and in these, corresponding additional corrections were made.

Electrocardiographic records. Lead II was used in all experiments and records were taken during the first and last minutes of each test period. The pulse rate was noted at frequent intervals in addition to the rates recorded on the electrocardiograms.

Animal Experiments

Large, quiet dogs were used. They were trained to lie on the dog board for fifteen to thirty-minute periods each day for four to seven days before they were used. They readily became accustomed to the mask and to breathing in the spirometer. On the day of the experiment, the dog was placed on the board and connections made for taking the electrocardiograms. The right femoral artery was exposed under procaine hydrochloride anesthesia. A gauze bandage saturated with petrolatum was placed around the dog's muzzle, or else it was shaved the day before and a rubber mask (Blalock (25)) was put in position and inflated. The mask was connected to the Sanborn Graphic apparatus and the dog permitted to rebreathe fifteen to twenty minutes before the test period was started. The test period of eight minutes was then recorded and arterial and venous blood collected at the end of this time.

After a satisfactory normal period, the dog was tied to the board and anesthetized as described above. Following twenty-five to forty minutes of anesthesia, usually of a moderate surgical stage with good abdominal relaxation but with the wink reflex present,

a second metabolic period was recorded, at the end of which arterial and venous samples were taken. The cyclopropane concentration in the spirometer at the beginning and at the end of the test period was determined. A 5 cc. sample of arterial blood was drawn and analyzed for the cyclopropane content

After the first determination under anesthesia, the cyclopropane content in the Sanborn Graphic was increased gradually until the wink reflex was abolished. The dog was then kept at this level for twenty to thirty minutes, after which a second determination was made.

Finally, the cyclopropane concentration was increased until the respiration ceased, at which time an arterial sample was collected for the determination of the cyclopropane present at respiratory arrest.

Results

The results obtained from a series of nine dogs are shown in table 35. The following general conclusions can be drawn from the data given·

1. The normal cardiac output per kilo per minute in seven of the nine experiments averaged 155 cc. which approximates the values given by Marshall (198) of 135 cc. and Blalock (25) of 159 cc. Special attention will be called to experiments 1 and 6 below.

2. The arterial oxygen content under anesthesia is greater than the normal by 2 volume per cent.

3. The arterial-venous oxygen difference is less under anesthesia than in the normal.

4. The cardiac output under moderate surgical anesthesia with cyclopropane, stage III, plane 3, is increased 45 per cent with an arterial concentration of cyclopropane which is equal to 62 per cent of the fatal concentration.

5. In four dogs in which the arterial content of cyclopropane averaged 85 per cent of the fatal amount, the output was equal to the normal.

6. In five dogs in which the arterial concentration of cyclo-

propane was 95 per cent of the fatal concentration, the output was reduced on the average of 28 per cent.

In experiment 1, the dog was pregnant and near term because one of the two fetuses lived for two months following delivery by section after the maternal respiration ceased. The elevated cardiac output in the control is explainable on the basis of the pregnancy as Burwell (56) reported a 50 per cent increase during the seventh and eighth months of pregnancy in normal women. In experiment 6, however, we have no explanation for the high normal output, but because the output under anesthesia was increased over the control, we feel that it is correct.

Special attention should be called to the results in experiments 5 and 8, in which output studies were made under a moderate depth of anesthesia thirty and sixty minutes, respectively, after determinations under very deep anesthesia. In experiment 5, the output returned from a decrease of 57 per cent to normal under a lighter anesthesia, and in number 8 from a decrease of 13 per cent to an increase of 16 per cent. These show that any decrease in the output which is present under a deep anesthesia rapidly reverts to normal or to an increase in output when the anesthesia is lightened.

No cardiac irregularities were noted in this study.

Blalock (25) in 1927 reported a study on the effect of ether anesthesia upon the cardiac output. He found that in dogs under moderate surgical anesthesia the output was increased 76 per cent, but under very deep anesthesia the output decreased to a value less than the normal. In later studies by Blalock (26) it was found that the output under chloroform anesthesia was decreased 28 per cent, and under ethyl chloride the changes were variable but averaged 14 per cent less than the normal. Marshall (197) reported that under pantopon-urethane anesthesia the output was increased 20 to 160 per cent but that under morphine alone there was no change in output. Calculation of data given by Moore *et al.* (218) in their studies on dogs under barbital anesthesia gives an average output per kilo per minute of 227 cc., which is about 50 to 60 per

cent greater than the average normal output values of Marshall (197) and of Blalock (25). In all of the studies mentioned above, the Fick principle was used in calculating the output after direct determination of the oxygen content of the arterial and venous blood.

Greisheimer and her associates (122) have made numerous studies on the effect of cyclopropane upon various cardiovascular functions in the normal dog, in the dog with morphine premedication, and in dogs that have had ether as a supplement either before or after cyclopropane anesthesia. They have not made control cardiac output studies on the dog in the awakened state. Their procedure is to anesthetize the animal very lightly, or moderately deep, make a determination, and continue the animal in this stage for a long period of time and make repeated examinations at ten to fifteen-minute intervals for six or eight times. In their report of 1954, Greisheimer, Ellis, Webber, Bayer, and Lynch (120) reported on the cardiac output by Cuvette oximeter under cyclopropane anesthesia. In a series of nineteen dogs, receiving cyclopropane alone, the average concentration of 18 to 18.5 mgm. of cyclopropane to 100 cc. of blood, they found the average cardiac output on their first determination to be 2.97 liters per sq. meter per minute. Approximately seventy-five minutes later, their sixth determination on the cardiac output with a concentration of 18 6 mgm. of cyclopropane per 100 cc. showed 3.56 liters per sq. meter per minute. Along with this slight increase in cardiac output as the anesthesia was maintained, they observed a slight fall in the cardiac rate from an average of 141 per minute to 127. There was a relatively constant blood pressure of 150 mm. throughout the study. They feel as time of anesthesia extends that there is a reduction in the peripheral resistance permitting a slight increase in the cardiac output as the blood pressure is maintained. Greisheimer *et al.* (119), in a subsequent study upon the cardiac output by Cuvette oximeter under cyclopropane-oxygen-ether anesthesia, found an increase in the output as anesthesia continued under cyclopropane with a concentration of 11.9 to 28 mgm. per 100 cc.

with an average of 19 mgm. per 100 cc., and in these same animals when the cyclopropane was reduced and ether added so that there were 9 mgm. of cyclopropane and 87 mgm. of ether, the cardiac output had increased from 3.1 liters per minute under cyclopropane alone to 4.3 liters per sq. meter per minute when the dogs were under a combination of cyclopropane and ether. They noted a marked increase in heart rate after the ether was added to the cyclopropane anesthetized dogs and also a fall in blood pressure from 146 mm. of mercury under cyclopropane alone to 115 mm. of mercury with cyclopropane and ether. This fall in blood pressure at the same time of the significant increase in cardiac output must indicate a reduction in peripheral resistance, and this is highly probable because the dogs have nearly a full anesthetic concentration of ether and approximately a half of an anesthetic dose of cyclopropane, so that under the mixture the animals must have been much deeper anesthetized than they were with the cyclopropane alone.

In a later paper by Greisheimer and her associates (118) upon the effect of thiopental sodium anesthesia, the cardiac output in fifty-one experiments was 4 liters per sq. meter per minute, whereas when cyclopropane was added to supplement the pentothal when the pentothal concentration was approximately half that in the pentothal alone experiments and cylcopropane was a little over half the anesthetic dose, they found the caidiac output had been reduced to 3.5 liters per sq. meter per minute. At the same time they observed a fall in heart rate from 196 per minute under thiopental sodium alone to 153 per minute under thiopental sodium and cyclopropane. In a more recent paper by Greisheimer and her associates (117) on the effect of morphine and cyclopropane anesthesia on the cardiovascular function in the dog, their animals were premedicated with 3 mgm. per kilo of morphine. This dose of morphine reduced the concentration of cyclopropane necessary for the given level of anesthesia from 19.7 mgm. to 9.9 mgm. per 100 cc. of blood. In the dogs that had received cyclopropane alone, they found an increase in the cardiac index from

cent greater than the average normal output values of Marshall (197) and of Blalock (25). In all of the studies mentioned above, the Fick principle was used in calculating the output after direct determination of the oxygen content of the arterial and venous blood.

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pressure of 4 cm. of water. With thiopental sodium of 50 mgm. in 500 cc. of the perfusion fluid, the cardiac output was decreased from 250 to 50 cc. per minute and the right auricular pressure increased from 0 to 17 cm. of water. These marked differences in the decrease in cardiac output and the increase in right auricular pressure in the heart-lung preparation must be due to a relative variation in the concentrations of the anesthetic agents, whereas 73 mgm. of ether per 100 cc. of blood or perfusion fluid are approximately three-fourths of the anesthetic dose, cyclopropane, 23 mgm. per 100 cc., is well beyond the anesthetic dose and is approximately four-fifths of the fatal concentration. Fifty mgm. of thiopental sodium per 500 cc. are far in excess of that which would be obtained in the body of a normal subject during anesthesia with thiopental sodium. In the second portion of their study, the cardiac output was determined in man under pentothal sodium, ether, and cyclopropane anesthesia. In their study on man, the spirogram method of oxygen consumption was used, and they spent considerable time in comparing this method with that of the Fick principle and feel that in their hands it is accurate. In addition to the cardiac output under these conditions they measured the forearm blood flow by the technic of Bancroft, and with ether and cyclopropane they determined the alterations in the right auricular pressure. Their values are shown in table 36. Particularly of interest in this table is the lack of change in cardiac output under pentothal anesthesia and the relatively large increase under ether and under cyclopropane anesthesia as this is the only report of an increase in cardiac output in man under cyclopropane anesthesia. This might be due in part to the increase in heart rate during anesthesia with cyclopropane after the induction with thiopental. The forearm blood flow increased with pentothal approximately threefold, that with ether fivefold, and with cyclopropane at least fourfold.

Lee *et al.* (180) have reported a study on the circulatory effects of prolonged light anesthesia in man in which six healthy male adults were used for the study. They carried out cardiac output

3.07 liters per minute on the first determination to 3.66 liters on the sixth determination, whereas when a dog has been premedicated with morphine, the first determination of the cardiac output was 1.8 liters per minute and at the sixth determination 2.8 liters per minute. Thus the addition of morphine to the dog reduced the cardiac output approximately a third, systolic blood pressure was down 20 per cent, the mean blood pressure had been reduced from 150 to 104 mm. of mercury, and the heart rate from 120 per minute to 71 per minute. Thus with dogs, morphine markedly decreases the cardiovascular function under cyclopropane anesthesia. From these studies of Gresiheimer and her associates, one may say that cyclopropane anesthesia of a constant level over a long period of time causes a slight rise in the cardiac output, a moderate fall in the heart rate, very little change in the blood pressure. However, when pentothal or morphine are added to the cyclopropane either before or after, there are a diminution of the cardiac output and a fall in blood pressure. These observations were on dogs, and the interpretation of their significance is of value only for the dog. In the dogs that received morphine followed with cyclopropane, they observed marked cardiac arrhythmias in over 50 per cent of the experiments. This had been noted first by Seevers and his associates (297) and later studied in more detail by Robbins, Baxter, and Fitzhugh (279).

Man. Prime and Gray (261) in 1952 reported a study upon the effect of certain anesthetics and relaxing agents on circulatory dynamics. In the first portion of their paper the study was devoted to the effect of ether, cyclopropane, and thiopental sodium upon the cardiac output and the right auricular pressure of the dog heart in the heart-lung preparation. In the ether experiments, the concentration of ether was 73 mgm. per 100 cc. of the perfusion fluid. This caused a decrease in cardiac output from 260 to 160 per minute and an increase in right auricular pressure of 2 cm. of water. With cyclopropane in the perfusion fluid in the concentration of 23 mgm. per 100 cc , the cardiac output was decreased from 200 to 70 cc. per minute with an increase of right auricular

pressure of 4 cm. of water. With thiopental sodium of 50 mgm. in 500 cc. of the perfusion fluid, the cardiac output was decreased from 250 to 50 cc. per minute and the right auricular pressure increased from 0 to 17 cm. of water. These marked differences in the decrease in cardiac output and the increase in right auricular pressure in the heart-lung preparation must be due to a relative variation in the concentrations of the anesthetic agents, whereas 73 mgm. of ether per 100 cc. of blood or perfusion fluid are approximately three-fourths of the anesthetic dose, cyclopropane, 23 mgm. per 100 cc., is well beyond the anesthetic dose and is approximately four-fifths of the fatal concentration. Fifty mgm. of thiopental sodium per 500 cc. are far in excess of that which would be obtained in the body of a normal subject during anesthesia with thiopental sodium. In the second portion of their study, the cardiac output was determined in man under pentothal sodium, ether, and cyclopropane anesthesia. In their study on man, the spirogram method of oxygen consumption was used, and they spent considerable time in comparing this method with that of the Fick principle and feel that in their hands it is accurate. In addition to the cardiac output under these conditions they measured the forearm blood flow by the technic of Bancroft, and with ether and cyclopropane they determined the alterations in the right auricular pressure. Their values are shown in table 36. Particularly of interest in this table is the lack of change in cardiac output under pentothal anesthesia and the relatively large increase under ether and under cyclopropane anesthesia as this is the only report of an increase in cardiac output in man under cyclopropane anesthesia. This might be due in part to the increase in heart rate during anesthesia with cyclopropane after the induction with thiopental. The forearm blood flow increased with pentothal approximately threefold, that with ether fivefold, and with cyclopropane at least fourfold.

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TABLE 36*

Effect of pentothal, ether, and cyclopropane upon the cardiac output, heart rate, forearm blood flow and right auricular pressure in man

No Patients	Condition	C O—L/1'	Heart Rate	F B F—cc /100	R A P
15	Control	4 8 ± .9	67 ± 5		
	After Premed	5.5 ± .8	71 ± 6	5.5	
	Pent Anes.	5. ± .7	87 ± 7	17 5	
10	After Premed.	6.1 ± 9	71 ± 7	6 9	−1.5
	Ether Anes.	8.4 ± 1.4	83 ± 5	30	−1
6	After Premed.	4 8	72	4 2	−1 5
	Cyclopropane Anes	8 1	77	17	0

* After Prime and Gray: Brit J. Anaesth , 24, 101–136, 1952 (261)

studies using the Evans blue dye method, alteration in kidney functions using inulin and para-aminohippurate, and also the alteration or change in the arm blood flow using the occlusion plethysmograph. Their subjects were given preanesthetic medication of omnopon 11 to 22 mgm. and scopolamine .4 to .65 mgm. As a rule the anesthesia was induced with a small dose of thiopental sodium and immediately changed thereafter to cyclopropane and oxygen mixture and maintained in stage III, plane 1, during the experimental study. They observed a decrease in cardiac output of approximately 30 per cent under anesthesia as compared to their control. The forearm blood flow was increased about 80 per cent under anesthesia. The glomerular filtration was decreased 50 per cent and the renal blood flow approximately 40 per cent under anesthesia at the beginning of the anesthesia with a gradual return toward the preanesthetic level as anesthesia was prolonged. These data are recorded graphically in figure 31 in Chapter 3, and figure 62 in Chapter 7.

DeWardener and his associates (85) report a study on the circulatory effects of hemorrhage during prolonged light anesthesia in man. They studied fourteen healthy subjects in which operations for correction of varicose veins were done. In place of determining

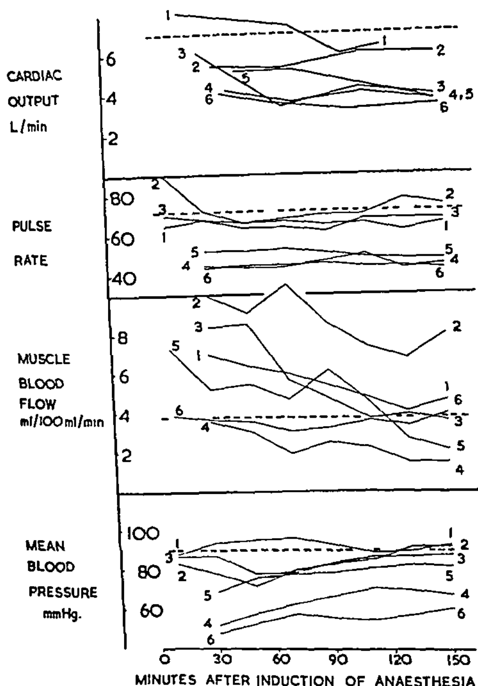


FIG 31 The effect of prolonged light cyclopropane anesthesia on the cardiac output, pulse rate, forearm blood flow, and blood pressure. The dotted lines represent an estimated mean value for normal conscious subjects. (Lee, Churchill-Davidson, Miles, and DeWardener Clin Sc, 12, 169, 1953)

the cardiac output in the awakened state, they waited and made their control studies after a light anesthesia had been induced. The patients were bled before the operative procedure of 13 to 29 per cent of the calculated blood volume, and the cardiac studies made ten to twenty minutes after the hemorrhage giving a little time for the readjustment due to the blood loss. Cardiac output after hemorrhage was reduced 33 per cent, the pulse rate was increased 10 per cent, the forearm muscle blood flow was reduced 58 per cent, and the blood pressure only 10 per cent. There was no significant change in the renal blood flow or glomerular filtration during or as a result of this hemorrhage.

In 1955, Etsten, Reynolds, and Li (94) published their studies upon the effects of controlled respiration on circulation during cyclopropane anesthesia. In their control studies the cardiac index was 3.5 liters per minute, that under light surgical anesthesia was 3.3 liters per minute, no significant change, but when the respiration was controlled the cardiac index fell from 3.3 to 2.5 liters per minute which is of marked significance. They felt that the increased intraairway pressure reduced the blood flow through the lungs thus cutting back the cardiac output. During their studies on controlled respirations they found that the carbon dioxide tension and oxygen was normal during the period of ventilation.

Li and Etsten (186), in 1957, published a study on the effects of cyclopropane anesthesia on the cardiac output and related hemodynamics in man In this study they correlated the concentration of cyclopropane in the blood with the electroencephalographic changes as one proceeded from light anesthesia to deep anesthesia. These results of their data on the cardiac index are shown in figure 32 and on the effect of the total peripheral resistance, the stroke volume, and the heart rate are shown in figure 33. It is of interest to note in figure 32 that as the depth of anesthesia progresses, there is a gradual return of the cardiac output to the preanesthetic level This they believe is due to a decrease in the peripheral resistance of the vascular bed as is shown in figure 33.

Etsten and Li (93) have studied the effect of chlorpromazine as a preanesthetic drug in place of morphine and scopolamine. In a group of fourteen subjects that received morphine and scopolamine as the preanesthetic drug, there was an average reduction of the cardiac index of 18 per cent during surgical anesthesia. With fourteen patients that received chlorpromazine as preanesthetic medication and given cyclopropane anesthesia, there was an increase of 7 per cent, which is not significant, but at least the change from morphine and scopolamine to chlorpromazine resulted in a better cardiac output during cyclopropane anesthesia. They believe that this is due to two factors. First, that with chlorpromazine the heart rate is not reduced as much with cyclopropane as it is following morphine and scopolamine premedication and cyclo-

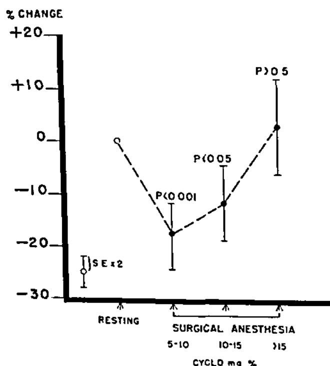


FIG 32 Cardiac index during cyclopropane anesthesia. The mean percentage change of the cardiac index obtained during each of three levels of cyclopropane anesthesia is compared with the value obtained during the resting state. (Li and Etsten. Anesthesiology, 18, 15, 1957)

propane anesthesia. Second, with cyclopropane following morphine and scopolamine there was a marked increase in the total peripheral resistance of 46 per cent above the control, whereas when chlorpromazine was given the increase was only 12 per cent.

Thompson, Patrick, and Woods (335) published a study early in 1957 on the effect of cyclopropane anesthesia on the circulation of human beings in which seven patients were the experimental subjects. They made observations on the cardiac output, the pulse, the blood pressure, and the peripheral resistance on these seven patients in three or four different planes of anesthesia as determined by the electroencephalogram. In contrast to the observa-

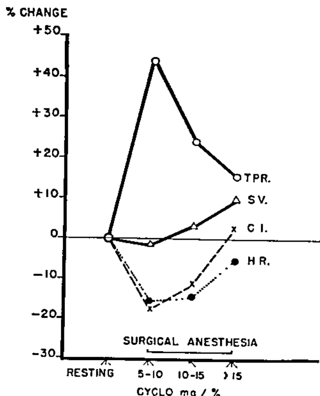


FIG 33. Hemodynamic changes during cyclopropane anesthesia T P.R = total peripheral resistance, S V. = stroke volume, C I = cardiac index, and H R. = heart rate The changes in the heart rate paralleled the changes in the cardiac index. (Li and Etsten Anesthesiology, 18, 15, 1957)

tions by Li and Etsten, Thompson and his associates found a continual increase in the peripheral resistance as the depth of anesthesia was increased, whereas Li and Etsten obtained first a marked increase in peripheral resistance, and as anesthesia was increased to the electroencephalographic level 4, they observed a return of the peripheral resistance toward the control value. Likewise, Thompson and his associates observed a continuous reduction in the cardiac output as the level of anesthesia was increased. This decrease in cardiac output was directly parallel to the decrease in the heart rate of the patients. Figure 34 shows the results of Thompson and his associates' study on the cardiac index, pulse rate, stroke index, and the radial arterial mean pressure.

It seems from the reports discussed above that the cardiac output in man under cyclopropane anesthesia is decreased from the control by somewhere around 20 per cent. Likewise, there is a diminution in the heart rate which parallels the decrease of cardiac output. These data were obtained in studies in which the Evans blue dye was used for the determination of cardiac output. In man the only study showing an increase of cardiac output during cyclopropane anesthesia is that of Prime in which the spirographic method of the determination of oxygen consumption was used. In the dog it seems that there is an increase in the cardiac output during surgical anesthesia of moderate degree, and that with very deep anesthesia there is a decrease in the cardiac output.

EFFECT OF CYCLOPROPANE ON WORK CAPACITY OF THE HEART

There have been other studies on the effect of cyclopropane on the cardiac mechanism or its ability to do work.

Lee *et al.* (181), in their study on the mechanism of production of spontaneous cardiac irregularities with high concentrations of cyclopropane, have reported upon the effect of perfusion of the dog and the cat heart with fluid containing various concentrations of cyclopropane, and they note a reduction in the ability of the heart to make a maximum contraction and also a slowing of the heart rate. A photograph of one of their records is shown in figure

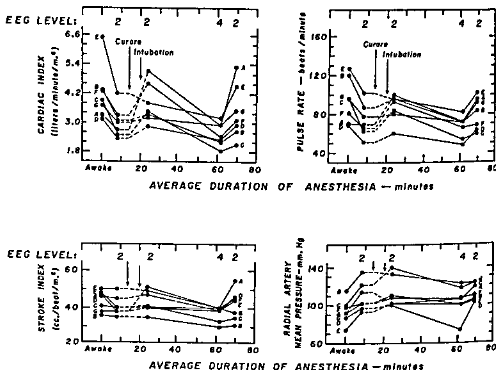


FIG 34 Graphs showing changes in cardiac index, pulse rate, stroke volume, and mean pressure in radial artery during cyclopropane anesthesia. Letters A to G represent cases 1 to 7 as listed in tables Solid dots represent average time at which observations were made, and values for individual patients are connected. Broken line represents average time taken to administer curare and intubate patient Cardiac index and pulse rate parallel each other closely with significant decrease in light anesthesia (electroencephalographic level 2) and further decrease in deep anesthesia (electroencephalographic level 4) and return toward values when awake on lightening level of anesthesia (Thompson, Patrick, and Woods J A M A , 164, 389, 1957)

35 in which the heart of the dog was perfused for a short period of time with fluid containing cyclopropane. During the period of perfusion there was a marked diminution in the contractility of the heart, and this was soon returned to normal upon the removal of cyclopropane from the perfusion solution.

Brace, Scherf, and Spire (38) in 1941 reported upon the effect of cyclopropane upon the blood pressure, stroke volume, and heart size of the dog. They prepared their animals for study under light

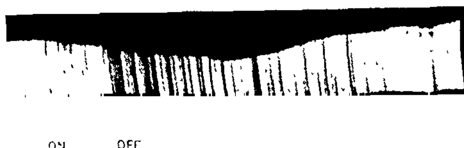


Fig 35. A record from a dog heart perfusion with defibrinated blood treated for control or cyclopropane tests as indicated. Cardiac depression by cyclopropane, followed by recovery after its withdrawal, is evident as was the case with other species tested (Lee, Orth, Wangeman, and Meek: Anesthesiology, 4, 487, 1943)

nembutal anesthesia and placed a plethysmograph around the heart including the ventricles and the base of the heart. This method showed alterations in the diastolic size of the heart. They administered relatively high concentrations of cyclopropane, 50 to 75 per cent cyclopropane in oxygen, for periods of five to eight minutes. As a rule there was an increase in blood pressure as the anesthesia proceeded, there was an increase in the diastolic size of the heart, and pulsus alternans was observed quite frequently when the 75 per cent mixture of cyclopropane was being used. Cardiac arrhythmias other than the pulsus alternans were never observed. With the 50 per cent mixture in the inspired air, they observed routinely an increase in blood pressure, an increase in the heart volume, also an increase in stroke size. They, like Lee, found that the heart returned to normal very rapidly after the administration of cyclopropane was discontinued. A photograph of one of their studies is shown in figure 36.

Moe and his associates (216) reported on the effect of cyclopropane on cardiac work capacity. Using the standard heart-lung preparation, they observed the effect of cylcopropane on the cardiac work capacity by determining the cardiac reserve as indicated by changes in the right auricular pressure when the aortic pressure is raised. Figure 37 is from their paper. It is observed that when cyclopropane in 10 mgm. per 100 cc. was used, the auricular pres-

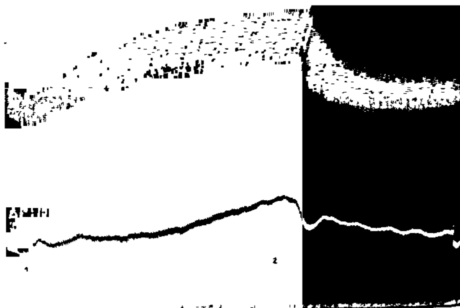


Fig 36 Blood pressure and cardiac plethysmogram during administration of a mixture of 50 per cent cyclopropane and 50 per cent oxygen (Brace, Scherf, and Spire Anesthesiology, 2, 261, 1941)

sure was increased from 50 to 96 mm. of water when the aortic pressure was increased from 86 to 106 mm. of mercury. When cyclopropane in concentrations of 20 mgm. per 100 cc. was perfused, the auricular pressure increased from 69 to 173 mm. of water when the aortic pressure was increased from 86 to 100 mm. of mercury. This shows a progressive decrease in the cardiac reserve as the concentration of cyclopropane was increased.

In a more recent study by Price and Helrich (260) upon the effect of cyclopropane, diethyl ether, nitrous oxide, thiopental and hydrogen ion concentrations on the myocardial function of the dog heart-lung preparation, it was found, with all of the anesthetic agents in their approximately equivalent anesthesia producing doses, that there was a diminution in the mechanical ability of the heart. The mechanical ability of the heart was calculated as the slope of the line relating cardiac output in liters per minute and the

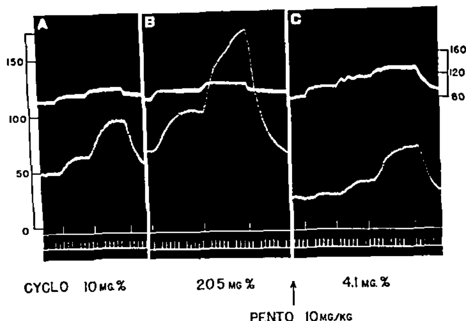


FIG 37. Experiment 1-24-49. Dog 10 3 kgm. Pressure stabilizer attached to abdominal aorta Tracings, top to bottom: arterial pressure, scale at right in millimeters of mercury; right auricular pressure, scale at left in millimeters of water; signal; time, 10 seconds Figures after "Cyclo" refer to cylcopropane concentration in jugular venous blood. Pento = pentobarbital sodium. Between B and C, cyclopropane discontinued, followed by frequent flushing for twenty minutes. (Moe *et al* · Anesthesiology, 10, 706, 1949)

right atrial pressure which was obtained when the heart was working against the fixed arterial pressure. Figure 38 is taken from their paper, and it can be readily seen that all of the anesthetic agents, even including nitrous oxide, when given in anesthetic concentrations produced a diminution in the ability of the heart to do work, and this diminution was more or less similar with all of the four anesthetic agents studied.

Price and his associates (259), in the study on change in the central venous and arterial pressures during anesthesia in man, observed an increase in the blood pressure of 11 mm. of mercury in stage III, plane 2, surgical anesthesia and a decrease in the heart rate in twelve of fifteen patients. Simultaneous observations on the central venous pressure showed that during cyclopropane

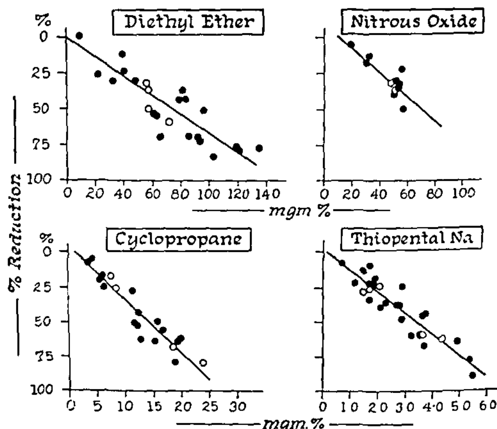


FIG. 38 Effect of anesthetic agents on the heart-lung preparation The mechanical function is reduced as the concentration of the anesthetic in the blood is increased (Price and Helrich J Pharmacol & Exper Therap., 115, 206, 1955)

anesthesia there was an increase in this pressure, whether the pCO_2 was up or not, but if the pCO_2 was increased, there was a more marked increase in the central venous pressure (fig. 39). They believe that the increased venous pressure is related to a diminution in the heart rate which in turn is related to the concentration of cyclopropane. They feel that cyclopropane may reduce the competence of the heart while at the same time augmenting the return of blood from the periphery.

CYCLOPROPANE UPON THE HEART RATE

In their earlier work, Waters and associates were of the opinion that cyclopropane in non-premedicated man and dog decreased

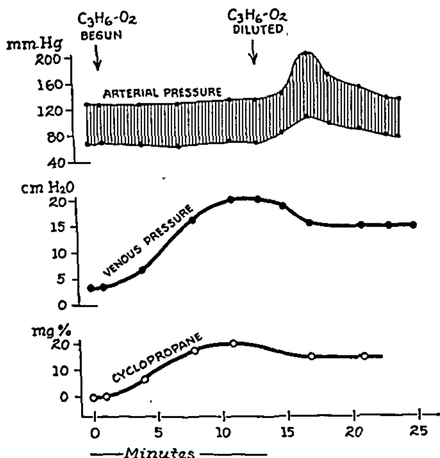


FIG. 39 The effect of a reduction in arterial blood concentration on the arterial and central venous pressure (Price, Conner, and Dripps Anesthesiology, 14, 1, 1952)

the heart rate, but later Seevers and Waters (298) felt that further experience does not support their former opinion in relation to the dog

Lee *et al.* (180), Li and Etsten (186), and Thompson *et al.* (335) all report a reduction of pulse rate in man during cyclopropane anesthesia.

Shackell and Blumenthal (299) found in monkeys that cyclopropane anesthesia decreased the heart rate and that the higher the concentration of cyclopropane, the greater the decrease as a rule.

In papers by Robbins and Baxter (275, 276, 277) it was recorded

TABLE 37*

The effect of premedication upon the heart rate and rhythm in dogs anesthetized with cyclopropane

Number of Dogs	Premedication		Control		After Premedication		III_{1-2}†		III_{3-4}†		IV†	
	Type	Mgm per kgm	Rate	Rhythm	Rate	Rhythm	Rate	Rhythm	Rate	Rhythm	Rate	Rhythm
27	None		120	S A 19 Reg 7 A V Bl 1			141	S. A 1 Reg. 25 A V. Dis. 1	149	S. A 1 Reg 21 Nodal 5	130	S A. 1 Reg. 21 Nodal 3
13	Trained dogs		87	S A 13			126	Reg 13	146	Reg 13		
4	Morphine	2	100	S. A 4	70	S A 4	56	S A. 2 V Ex 2	57	V. Ex. 4 Nodal 1		‡
13	Morphine	5	135	S. A. 10 Reg 2 V. Ex. 1	73	S A. 10 V. Ex 3	68	S A 3 V Ex. 9 Nodal 4	65	S A. 1 V Ex. 11 Nodal 5		‡
4	Amytal	10	91	S A. 4	148	Reg. 4	159	Reg. 4	162	Reg. 3 V. Ex 1	151	Reg. 2 V. Ex. 1
6	Amytal	30	102	S A. 5 Nodal 1	170	Reg. 6	170	Reg. 6	177	Reg. 6	213	Reg. 6
4	Amytal	45	96	S A. 4	179	Reg. 4	177	Reg. 4	150	Reg. 4	150	Reg 4

* Robbins and Baxter: J. Pharmacol. and Exper. Therap., 68, 85, 1940 (277).

† Stages of anesthesia after Guedel.

‡ These dogs were given amytal sodium, 2.5 mgm per kilogram, intravenously while in stage III_{3-4} to abolish the cardiac irregularities.

S. A = sinus arrhythmia; Reg. = regular; A. V. Bl. = auriculoventricular block; A V. Dis = auriculoventriclar dissociation; Nodal = nodal rhythm or nodal extrasystoles, V Ex. = ventricular extrasystoles. The number after the abbreviation is the number of dogs showing that type of rhythm.

that in non-premedicated, untrained and trained dogs the heart rate was greater under cyclopropane anesthesia than in the pre-anesthetic state.

The average heart rate values in seventy-one dogs with and without premedication are shown in table 37.

Cyclopropane alone increases the heart rate in all planes of anesthesia in dogs; morphine reduces the control rate which is maintained or further reduced under cyclopropane; amytal alone causes an increase in the rate which is maintained with cyclopropane so that it is in the range of those with cyclopropane alone.

CYCLOPROPANE UPON THE BLOOD PRESSURE

There is a difference of opinion reported in the clinical literature regarding the effect of cyclopropane anesthesia upon the blood pressure. Waters (339) and Marshall and Daly (201) state that there is little or no change; Rovenstine (286) states that there is a slight fall in thoracic cases, whereas Rowbotham (288) states that there is a consistent rise of 10 to 40 mm. of mercury. In most of the reports it was stated that the patients received morphine and atropine or scopolamine thirty to ninety minutes before the cyclopropane was started, some give a barbiturate in addition to the morphine about two hours before the anesthesia.

The studies of Dripps (89) in 1947 and Buckley in 1953 (43) show that the rise in pressure during cyclopropane is due to carbon dioxide accumulation and with adequate respiratory exchange the pressure remains normal.

Robbins and Baxter (277) reported a study in which the changes in blood pressure were recorded in fourteen dogs without premedication, fourteen with morphine premedication, and four dogs with amytal premedication. Their results are shown in table 38.

As a rule there was an increase in blood pressure in the non-premedicated dog, and this increase was maintained until the stage of respiratory arrest. This rise is not due to an increase of carbon dioxide content as postulated by Waters (339) because blood gas analyses failed to show an increase in carbon dioxide

TABLE 38*

The effect of premedication upon the blood pressure of dogs anesthetized with cyclopropane

Number of Dogs	Premedication		Blood Pressure				
	Type	Mgm per kgm	Control	After premedication	III_{2-3}	III_{3-4}	IV
14	None		115		130	130	122
5	Morphine	1	137	120	113	104	†
4	Morphine	2	149	135	110	108	†
5	Morphine	5	142	122	100	96	†
4	Amytal	10	137	139	135	134	133

* Robbins and Baxter: J Pharmacol and Exper. Therap., *68, 85, 1940 (277)*

† These dogs were given amytal sodium, 2.5 mgm. per kilogram "IV", while in stage III_{3-4} to abolish the cardiac irregularities.

TABLE 39

The effect of cyclopropane anesthesia upon the heart rate and rhythm and blood pressure in non-premedicated dogs

Experiment 21. Dog, 18 6 kgm , ♀—5/17/37

Time	Procedure or Stage	Blood Pressure	E K G Analysis				
			Number	Rate	P-R	T	Rhythm
9 34	Control	125	1*	80	.1	+	S. A.
9.44	C_3H_6 on						
9 44 5		*150*	*2*	*160*	*.09*	+	*S A.*
9·48	III_{2-3}	144	5	150	1	−	Regular
10 15	III_3	140	7*	110	.1		Regular
10 30	III_{3-4}	140	8*	110	.1		Regular
10 50	III_{3-4}	155	9	140	09		Regular
11 00	III_{3-4}	130	10	70	.11	−	Regular
11 03	III_4	120	11	50	09	−	Regular
11.05	IV	110	12*	55	10	−	Regular
11.08	IV	96	13	60	08	−	Regular
11.21	IV	60	15*	105	09	−	Regular
11·21.5	IV	60	16*	110	.10	+	Regular
11:22	IV	60-0	17*	110	.09	+	Regular
11 22 5	IV	0	18*	115	.10	+	Regular

* See figure 41 for electrocardiographic record See figure 40 for blood pressure *records*

until stage III_4 or stage IV was reached. In the dogs receiving morphine, the morphine alone produced a fall in blood pressure, and this fall was increased under cyclopropane; in the dogs receiving amytal, the blood pressure maintained a constant level throughout anesthesia but at respiratory arrest was slightly under the control level.

Protocols, kymographic records of blood pressure and respiration, and electrocardiographic records of several experiments on dogs anesthetized with cyclopropane alone and after premedication with morphine or amytal are given below.

Records from a non-premedicated dog, experiment 21, are given in table 39 and figures 40 and 41, and from another experiment, in table 40 and figures 42 and 43. In both experiments there was a rise of blood pressure during stage III, planes 2 and 4, and this

TABLE 40*

The effect of cyclopropane anesthesia upon the heart rate, rhythm, and blood pressure

Experiment 23 Pup, 7 2 kgm , ♂—5/25/37. Circle filter

Time	Procedure or Stage	Blood Pressure	EKG Analysis				
			Number	Rate	P R	T	Rhythm
9.44	Control	110	1†	140	1	+	S. A.
9·45	C_3H_6 on						
9.48	III_2	130	2	250	08	+	Regular
9·52	III_2	140	4	220	.08		Regular
9.54	III_2	115	6	260		−	Irregular
10:15	III_3	110	7†	130	.1	+	Regular
10 20	III_3	100	8	120	.1	+	Regular
10 30	III_3	110	9†	120	.1	+	Regulra
10:48	III_{3-4}	120	10†	135	.1	+	Regular
11.00	III_4	125	11†	130	.1	+	Regular
11:06	IV						
11 07 5	IV	70	12†	90	.1–.12	+	Nodal at end

The O_2 content at 11.07 was .5 volumes per cent.

* Robbins and Baxter J Pharmacol. and Exper. Therap., 68, 85, 1940 (277).

† See figure 43 for electrocardiographic records. See figure 42 for blood pressure records

TABLE 38*

The effect of premedication upon the blood pressure of dogs anesthetized with cyclopropane

Number of Dogs	Premedication		Blood Pressure				
	Type	Mgm per kgm	Control	After premedication	III_{2-3}	III_{3-4}	IV
14	None		115		130	130	122
5	Morphine	1	137	129	113	101	†
4	Morphine	2	149	135	110	108	†
5	Morphine	5	142	122	100	96	†
4	Amytal	10	137	139	135	134	133

* Robbins and Baxter J Pharmacol. and Exper. Therap , 68, 85, 1940 (277).

† These dogs were given amytal sodium, 2 5 mgm. per kilogram "IV", while in stage III_{3-4} to abolish the cardiac irregularities.

TABLE 39

The effect of cyclopropane anesthesia upon the heart rate and rhythm and blood pressure in non-premedicated dogs

Experiment 21. Dog, 18 6 kgm , ♀—5/17/37

Time	Procedure or Stage	Blood Pressure	E K G Analysis				
			Number	Rate	P-R	T	Rhythm
9:34	Control	125	1*	80	.1	+	S A.
9 44	C_3H_6 on						
9.41 5		150	2	160	09	+	S A.
9:48	III_{2-3}	144	5	150	1	–	Regular
10.15	III_3	140	7*	110	1		Regular
10 30	III_{3-4}	140	8*	110	.1		Regular
10.50	III_{3-4}	155	9	140	09		Regular
11·00	III_{3-4}	130	10	70	11	–	Regular
11 03	III_4	120	11	50	09	–	Regular
11·05	IV	110	12*	55	.10	–	Regular
11:08	IV	96	13	60	08	–	Regular
11:21	IV	60	15*	105	.09	–	Regular
11:21.5	IV	60	16*	110	10	+	Regular
11:22	IV	60-0	17*	110	.09	+	Regular
11:22.5	IV	0	18*	115	.10	+	Regular

* See figure 41 *for electrocardiographic record* See figure 40 *for blood pressure* records.

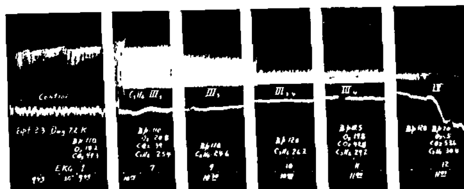


FIG. 42 Experiment 23 Record of blood pressure and respiration during cyclopropane anesthesia. See table 40 and figure 43 for further data on this experiment. (Robbins and Baxter· J. Pharmacol & Exper. Therap , 68, 85, 1940)

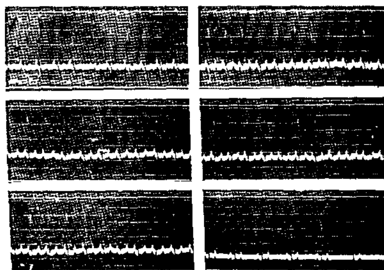


FIG 43. Electrocardiographic records from experiment 23. See table 40 and figure 42 (Robbins and Baxter. J. Pharmacol. & Exper. Therap., 68, 85, 1940)

rise of pressure was not due to an accumulation of carbon dioxide or to oxygen lack. There were occasional respiratory movements (of abdominal type) by the dog in experiment 21 after the electrocardiographic record no. 12 was made at 11:05 A.M.; these account for the long delay in the development of circulatory failure which was observed at 11:22 A.M. although the electrocardiographic record at this time was normal except for a marked increase in amplitude of the T wave (fig. 41, record no. 17).

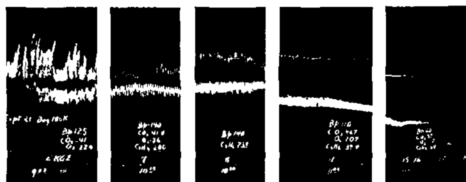


Fig. 40. Experiment 21. Record of blood pressure and respiration during cyclopropane anesthesia See table 39 and figure 41 for further data on this experiment

Fig. 41 Electrocardiographic records from experiment 21. See table 39 and figure 40

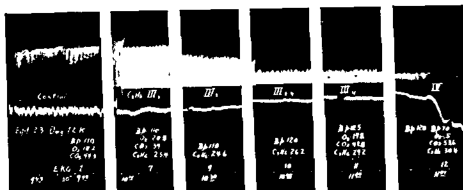


FIG. 42. Experiment 23. Record of blood pressure and respiration during cyclopropane anesthesia. See table 40 and figure 43 for further data on this experiment. (Robbins and Baxter J. Pharmacol & Exper. Therap., 68, 85, 1940)

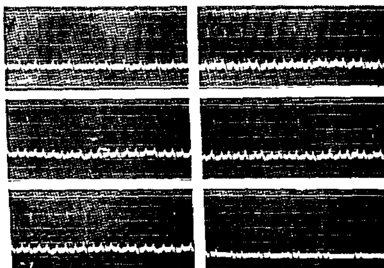


FIG 43. Electrocardiographic records from experiment 23. See table 40 and figure 42. (Robbins and Baxter· J. Pharmacol & Exper Therap., 68, 85, 1940)

rise of pressure was not due to an accumulation of carbon dioxide or to oxygen lack. There were occasional respiratory movements (of abdominal type) by the dog in experiment 21 after the electrocardiographic record no. 12 was made at 11:05 A.M.; these account for the long delay in the development of circulatory failure which was observed at 11:22 A.M. although the electrocardiographic record at this time was normal except for a marked increase in amplitude of the T wave (fig. 41, record no. 17).

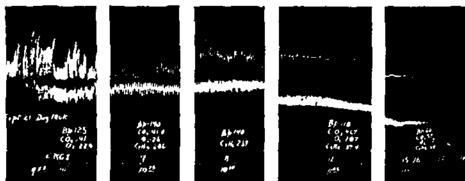


FIG 40. Experiment 21. Record of blood pressure and respiration during cyclopropane anesthesia. See table 39 and figure 41 for further data on this experiment.

FIG. 41 Electrocardiographic records from experiment 21. See table 39 and figure 40

Records from an experiment are given below in which the dogs received morphine as preanesthetic medication. In these dogs the blood pressure was reduced, the heart rate reduced, and cardiac irregularities were observed during stage III_{2-4} ; small doses of amytal were given while the irregularities were present, and routinely the rhythm returned to normal, and there was frequently a rise in blood pressure. See table 41 and figures 44 and 45.



FIG. 44 Experiment 8. Record of blood pressure and respiration during cyclopropane anesthesia See table 41 and figure 45 for further data on this experiment

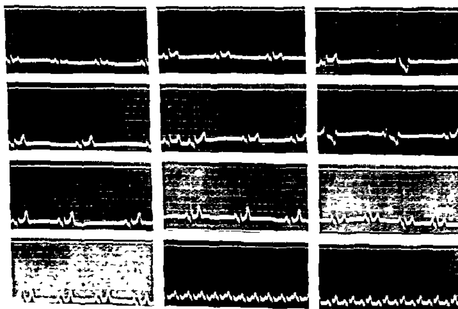


FIG 45 Electrocardiographic records from experiment 8. See table 41 and figure 44

TABLE 41

The effect of cyclopropane anesthesia upon the heart rate, rhythm, and blood pressure in dogs premedicated with morphine

Experiment 8. Dog, 14.5 kgm , ♀—2/7/39

Time	Procedure or Stage	Blood Pressure	EKG Analysis				
			Number	Rate	P-R	T	Rhythm
1.58	Control	170	1*	70	.11	+	S. A.
1.59	Morphine SO_4 , 2 mgm per kgm., subcutaneously						
2:29		160	2*	54	.11	+	S. A.
2:30	C_3H_6 on						
2:41	III_{2-3}	120	3	50	.13	+	S. A. marked
2:46	III_3	120	4	48	.14	+	S. A.; V. Ex.
2:50	III_3	110	6*	45	.13	+	S A.; V Ex
2·50 5	Amytal, 1 mgm per kgm., intravenously						
2:53	III_4	100	7*	42	.12	+	Regular
2·57	III_4	110	8*	60	.12	+	S. A
3 18	III_3	120	9	60	.13	+	S A.
3 28	III_4	100	10*	42		–	V. Ex.
3·29	Amytal, 1 5 mgm per kgm , intravenously						
3 31	III_4	120	11*	50	.12	+	Regular
3 37	III_4	120	12	60	11	+	Regular
3.45	III_4	115	13	65	11	+	Regular
3:50	III_{3-4}	120	14*	50	.11	+	Regular
3·51	Amytal, 7 5 mgm per kgm , intravenously						
4 00	III_4	125	15	140	.11	+	Regular
4.03	III_4	125	16	115	.11	+	Regular
4:15	III_3	130	19*	95	11	+	S. A.
4:24	III_4	125	20*	70	11	+	Regular
4:25	Atropine, 3 mgm per kgm , intravenously						
4:26	III_4	145	21*	210	1	+	Regular
4:30	IV	150				–	
4:36	IV	160				–	
4:42	IV	40	22*	240		+	Regular

* See figure 45 for electrocardiographic record See figure 44 for blood pressure records

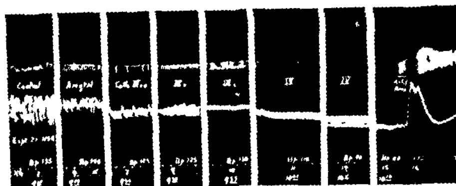


FIG. 46. Experiment 21. Record of blood pressure and respiration during cyclopropane anesthesia. See table 42 and figure 47 for further data on this experiment. (Robbins and Baxter: J. Pharmacol. & Exper. Therap., 68, 85, 1940)

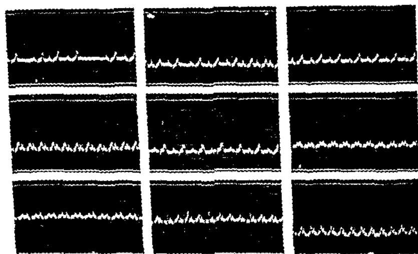


FIG. 47 Electrocardiographic records from experiment 21. See table 42 and figure 46 (Robbins and Baxter J Pharmacol & Exper. Therap., 68, 85, 1940)

the period of anesthesia is that of the blood flow to various areas of the body. Numerous studies have been made upon the alteration in blood flow to different areas of the body, that is, from the mesentery of the intestinal tract to the duration of blood flow from a small stab wound on the skin to the alteration in the blood flow through the hand or through the arm, through the foot or through the muscles of the calf.

The simplest of these methods, particularly from the technic of carrying out the observations, is the determination of the

TABLE 42*

The effect of cyclopropane anesthesia upon the heart rate, rhythm, and blood pressure in a dog premedicated with amytal

Experiment 21. Dog, 11.4 kgm., ♂—3/29/39

Time	Procedure or Stage	Blood Pressure	E K G. Analysis				
			Number	Rate	P-R	T	Rhythm
9:14	Control	135	1†	80	.10	+	S. A.
9:16–18	Amytal, 10 mgm per kgm., intravenously						
9:29		142	4†	150	10	+	S. A.
9:30	C_3H_6 on						
9:31	C_3H_6 on	170	5	270	07	+	Few V. Ex
9:34	*C_3H_6 on*	*160*	*6*	*300*	*.07*	+	*Regular*
9:44	III_{3-4}	125	7†	120	.12	+	Regular
9:49	III_4	125	8	140	.10	+	Regular
9:50	III_4	125	9	200	.09	+	Regular
9:55	III_3	130	10†	190	.10	+	Regular
10:02	IV	110	11†	120	.10	+	Regular
10:04	IV	105	12	160	.10	+	Regular
10.05	IV	110	13	180	.10	+	Regular
10:11	IV	96	14†	210	.09	+	Regular
10:14	IV	80	15†	170	.10	+	Regular
10:14 5	C_3H_6 off Artificial respiration, air						
10.15	III_3	170	16†	220	.10	+	
10:16	III	105	17†	240	.09	+	Regular

* Robbins and Baxter J Pharmacol and Exper Therap, 68, 85, 1940 (277).

† See figure 47 for electrocardiographic records. See figure 46 for blood pressure records

Data from an experiment in which amytal was given as a preanesthetic agent are given in table 42 and figures 46 and 47. Note the difference between these data and those obtained from the dog after morphine premedication

EFFECT OF CYCLOPROPANE UPON BLOOD FLOW IN CUTANEOUS AND DEEP BLOOD VESSELS

Another function of the cardiovascular system, primarily that in relation to the vessels, that can be studied before and during

studies on dogs using ether, cyclopropane, and pentothal as the anesthetic agents and the effect of the varying degrees of hemorrhage upon the alteration in blood flow through the smaller arterioles and capillaries as observed during microscopic visualization of the peripheral vessels. They conclude that during ether anesthesia and hemorrhage there is a greater deviation of the vascular control from the normal than there is with pentothal and that under cyclopropane anesthesia they observed no undesirable hemodynamic effects. They contrasted their observations in dogs with those in patients under similar anesthetic technics and during hemorrhage and feel that there is a satisfactory correlation between the harmful effect of ether upon the dog in shock as well as man in shock, and that the relative lack of undesirable effects of cyclopropane in the human subject in shock is similar to that in the dog where no undesirable effects were observed.

Hershey and Zweifach (149) in a subsequent study on peripheral vascular hemostasis in relation to anesthetic agents report their observation on thirty dogs in which ten dogs were used under each of the three anesthetic agents—cyclopropane, ether, and pentothal. They maintained their animals in the first plane of surgical anesthesia, and during this anesthesia they opened the abdomen and observed the vascular bed in the omentum and produced shock or marked blood loss in the dogs by first removing two per cent of their body weight of blood and at fifteen to twenty-minute intervals thereafter removing two-tenths to five-tenths per cent of their body weight of blood until the arterioles contained no further blood. With continuous microscopic observation of the vascular bed they were able to note the reaction of the different vessels, the arterioles, the veins and venules to the effect of blood loss and to compare these observations under the different anesthetic agents. They conclude that on the specific vasomotor mechanisms concerned, cyclopropane exerted little influence; pentothal had an intermediate effect, and ether a drastic, unfavorable effect.

In a more recent paper, Hershey and his associates (151) have

bleeding from the cut skin and subcutaneous tissues during anesthesia. This technic involves a small wound on the skin immediately above the nail bed of the finger, the application of a venous occlusion cuff inflated to a pressure of 40 mm. of mercury on the forearm, the collection of blood from the small skin puncture on filter paper at fifteen-second intervals, and measuring the area of the blood wetting upon the filter paper and determining the total area that is obtained in the given unit of time.

Cutaneous. McLoughlin (206) in 1954 reported the results of his study on the effect of cyclopropane on increasing cutaneous bleeding as compared to that of ether during light and deep anesthesia, and also during spontaneous and supplemental respiration in the deeper planes of cyclopropane anesthesia. These studies were carried out upon man, and each subject was his own control. Considering the amount of blood loss during the control period as one, during ether anesthesia two and six-tenths times as much blood was lost, whereas during cyclopropane anesthesia in lighter planes four times as much blood was lost as during the control period. McLoughlin observed that during the third and fourth plane of anesthesia with cyclopropane the blood loss was very large in comparison to the control or to that during plane 1 of surgical anesthesia. He gave several subjects supplemental breathing during the deep anesthesia, and this technique reduced the amount of blood loss; he felt that carbon dioxide accumulation was the cause of this increased blood loss during the period of the inadequate respiration in stage III, planes 3 and 4, of cyclopropane and suggested in his paper that supplemental respiration would prevent this cutaneous blood loss.

Mesentery. Hershey and his associates have reported numerous studies on the effect of anesthetics on the size of the arteriolar and capillary bed in the mesentery as well as the blood flow through these areas as determined by visual observation and photography. In 1945, Hershey and his associates (150) published a paper on the peripheral circulatory reactions as the basis of evaluating anesthetic agents In this paper are reported their

anesthesia. By comparison then, it required two to three minutes for a reversion of the depressant effects of deep cyclopropane anesthesia, approximately twenty minutes for that of deep ether anesthesia, and with pentothal the reversion occurred in about twenty-five minutes after the cessation of its administration. These observations definitely show that the depth of anesthesia is a factor in the alterations of the peripheral vasomotor function.

In the study by Bennett, Bassett, and Beecher (19) on the influence of ether, cyclopropane, or sodium evipal anesthesia upon the circulation under normal and shock conditions, in which they measured the blood flow in various portions of the vascular bed and determined the effect upon repeated deepening and lightening of the anesthetic during the experimental study, it was observed that with repeated cyclopropane there were no undesirable effects upon the circulatory mechanism, and that during the study in the shocked animal deepening the cyclopropane anesthesia did produce a reduction in blood pressure. However, this decrease was soon returned to normal on lightening the anesthetic so that in the shocked animal even cyclopropane had no prolonged undesirable effect on the circulatory system.

Foot, calf, and hand. Lynn and Shackman (192) have reported studies on the peripheral circulation during general anesthesia and surgery in which they measured the relative blood flow in the foot, calf, and hand. These studies were done under cyclopropane anesthesia, but the patients were first put to sleep with a small amount of thiopental sodium. Early during the cyclopropane anesthesia and the surgical procedures, the increase in blood flow through both the calf and the foot was approximately three to three and one-half times the control, whereas as the operative procedure persisted and the duration of anesthesia increased, there was a return to the normal or preoperative blood flow through both the foot and the calf. These were the average results obtained on fifteen cases undergoing major abdominal surgery. They feel that this early peripheral vasodilatation is a result of the anesthetic upon the vasomotor center and that the final re-

reported on the effects of the depth of anesthesia on behavior of peripheral vascular bed. Using their same technique of microscopic observation of the vascular bed of the omentum and running blood pressure records on the dogs, they studied the effects of light, moderate, and deep anesthesia on the vascular bed during cyclopropane anesthesia, pentothal anesthesia, and ether anesthesia. With cyclopropane they observed satisfactory vasomotor responses during light and moderate anesthesia; but when the depth was increased to third or fourth plane anesthesia, the responses were not as active as the controls. They shifted from the light to deep anesthesia repeatedly, and observed that there was a return from the undesirable effect of deep anesthesia to the satisfactory results upon lightening the anesthesia and that the recovery was as rapid after repeated changes as it was after the first observation. Light pentothal narcosis failed to interfere to any extent with the activities of the peripheral vascular mechanism. During deep pentothal anesthesia there was a depression of the different peripheral circulatory end points, that is, vasomotion, capillary venous outflow, and arterial tone were depressed. An average total dose of 25 mgm. per kilo in the dog produced very marked depression of the peripheral circulatory mechanism and a fall in systolic blood pressure from 120 mm. to 65 mm. of mercury. There was complete suppression of the vasomotion, venous return was sluggish, and there was a general arteriolar dilatation. The return to a satisfactory vasomotor response after the cessation of the administration of the pentothal required approximately twenty-five minutes. With light surgical anesthesia with ether, there were no undesirable peripheral circulatory effects. As the anesthetic was deepened with ether, there was a suppression or disappearance of vasomotion and the circulation through the capillary bed was slow; arteriolar dilatation was marked and the systolic blood pressure fell to 90 mm. of mercury. After the ether anesthesia was lightened, there was a period of approximately twenty minutes before there was a reversion of the vasomotor functions to the level that was present under light

anesthesia. By comparison then, it required two to three minutes for a reversion of the depressant effects of deep cyclopropane anesthesia, approximately twenty minutes for that of deep ether anesthesia, and with pentothal the reversion occurred in about twenty-five minutes after the cessation of its administration. These observations definitely show that the depth of anesthesia is a factor in the alterations of the peripheral vasomotor function.

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duction in blood flow through the extremities is due to a vasoconstriction at the end of the surgical procedure as a result of the attempt of the body to readjust circulatory function in order to maintain a relatively normal blood pressure.

Kitchen and his associates (169) made an attempt to determine the mechanism by which alteration in the blood flow to the forearm was altered during anesthesia. These studies were made on

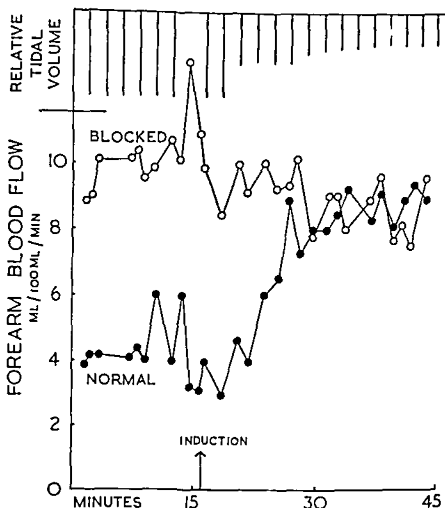


FIG. 48 The vasodilator action of light anesthesia on the normal arm and the absence of any change in blood flow in the nerve blocked forearm (Kitchen *et al*. Clin Sc, 12, 361, 1953)

seven human subjects, and the method of studying the blood flow was by the occlusion plethysmograph technic. In each subject the median, radial, and ulnar nerves were blocked at the elbow on one side and the other arm left with normal innervation. Thus each subject provided his own control. In the preanesthetic study, the normal flow was 3.65 cc. per 100 cc. of tissue, whereas in the arm that had the nerve block the preanesthetic flow was 9.6 cc. During light surgical anesthesia with cyclopropane on the normal side the flow was 6.6 cc. or approximately twice the control level, and on the side with the nerves blocked the flow was 9.66 cc. which is identical to preanesthetic reading. As they produced very deep anesthesia in these subjects, the blood flow was reduced in the normal arm to 2.6 cc. and in the arm with the nerve blocked to 3.85 cc. Results of their studies on the subject are shown in figure 48.

SUMMARY

Changes in the heart as shown by electrocardiographic records are rarely observed in non-premedicated dogs until respiration is so depressed that anoxemia is severe.

Under artificial respiration, the blood cyclopropane can be increased some 30 per cent over that necessary to produce respiratory arrest without electrocardiographic changes.

The irritability of the automatic tissues of the heart is increased by cyclopropane anesthesia.

Dogs anesthetized with cyclopropane after premedication with morphine show the same types of electrocardiographic changes as those most frequently observed in man under cyclopropane anesthesia after morphine and atropine or scopolamine premedication.

Dogs anesthetized with cyclopropane after premedication with barbiturates do not show electrocardiographic changes until long after respiratory arrest.

The spontaneous arrhythmia regularly observed in the cat during cyclopropane anesthesia is not dependent upon an intact

duction in blood flow through the extremities is due to a vasoconstriction at the end of the surgical procedure as a result of the attempt of the body to readjust circulatory function in order to maintain a relatively normal blood pressure.

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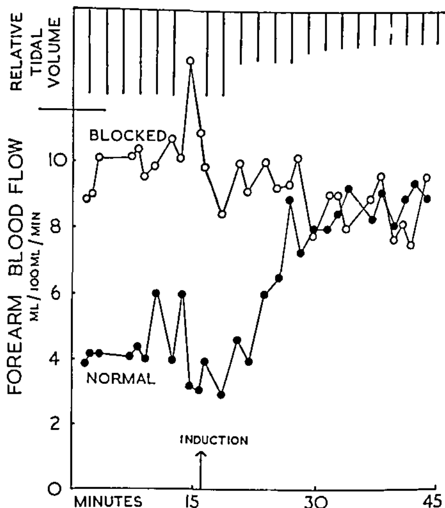


FIG 48 The vasodilator action of light anesthesia on the normal arm and the absence of any change in blood flow in the nerve blocked forearm (Kitchen *et al.*: Clin Sc, 12, 361, 1953)

4

The Effects of Cyclopropane Anesthesia Upon the Respiratory System

Cyclopropane, in contrast to ether and the other volatile anesthetics, has very little irritant action upon the mucosa of the respiratory tract, and for this reason the patient has no reflex protective mechanism against the inhalation of excessively high concentrations as he has against ether. Waters and Schmidt (341) and Romberger (283) state that concentrations up to about 50 per cent are without irritant action.

Robbins (271) reported that the irritant action of cyclopropane was much less than that of ether or chloroform as estimated by changes in the amount of salivary secretion in dogs during induction of and recovery from anesthesia by these agents; N_2O and ethylene failed to increase salivary secretion during induction or recovery. He showed that salivary secretion (parotid gland) was abolished during surgical anesthesia produced by ether, chloroform, nitrous oxide, ethylene, cyclopropane and barbiturates, but that during induction and recovery with ether and $CHCl_3$ the secretion was about five times the normal, with C_3H_6 the increase was about two and one-half times the normal.

The secretion of other glands in the oral and respiratory mucosa is not abolished during anesthesia because Waters (339) and others (201) comment upon mucus accumulating in the trachea and bronchi during anesthesia.

EFFECT OF CYCLOPROPANE UPON THE RATE AND AMPLITUDE OF RESPIRATION

Due to the relative lack of irritation with cyclopropane and the abundant supply of oxygen in the anesthetic mixture, the

sympathetic innervation to the heart, and the arrhythmia may be returned to a regular rhythm by an intravenous injection of a barbiturate (amytal).

The spontaneous arrhythmias frequently observed in man during cyclopropane anesthesia may be terminated by active supplementation of the respiratory exchange, by dilution of the anesthetic with oxygen, or by the intravenous injection of a barbiturate (secobarbital).

The cardiac output in non-premedicated dogs is increased in stage III_{1-3} with cyclopropane but decreased in stage III_{3-4}.

The cardiac output in man is decreased during cyclopropane anesthesia, and the change is parallel to the change in heart rate according to most observers.

The heart rate is increased in non-premedicated dogs under cyclopropane anesthesia; in morphine premedication the rate is decreased as it is in man; in barbiturate premedication the rate is higher than normal.

Cyclopropane anesthesia produces a rise in blood pressure in dogs without premedication, a fall after morphine, and no change after barbiturates; in man, various reports give a rise; others, a fall.

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EFFECT OF CYCLOPROPANE UPON THE RATE AND AMPLITUDE OF RESPIRATION

Due to the relative lack of irritation with cyclopropane and the abundant supply of oxygen in the anesthetic mixture, the

increase in rate and amplitude of respiration as observed with ether, ethylene, and N_2O due to irritation and oxygen lack is not present in patients anesthetized with cyclopropane and oxygen.

In Cat and Dog

In the early reports by Henderson and Lucas (146), the rate, volume, and minute volume of respiration were recorded on cats and dogs after anesthesia had been induced; it was found that as the concentration of cyclopropane was increased, the minute volume decreased markedly, while the rate increased. Figure 49 is from Henderson and Lucas (147) and shows the effect of cyclopropane on respiration and blood pressure. The tidal exchange was cut more than one-half. Results from two of their experiments are given in table 43.

The cat seems to be particularly susceptible to respiratory depression with cyclopropane.

Data from our own work on trained dogs, in which the rate, volume, and minute volume were determined by use of a Sandborn Graphic Metabolimeter in the control state and during dif-

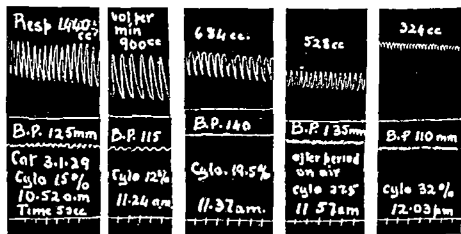


FIG. 49 Effect of increasing concentrations of cyclopropane upon the rate, tidal volume, minute volume of respiration and upon the blood pressure in the cat (Henderson and Lucas Arch internat de pharmacodyn. et de thérap., 37, 157, 1930)

TABLE 43*

Changes in the respiratory minute volume in animals under cyclopropane

	Cyclopropane	Rate	Volume	Minute Volume
	per cent		*cc*	*cc.*
Cat	12	15	60	900
	19	18	38	684
	27	33	16	528
	32	54	6	324
Dog	21	130	50	6500
	13	62	55	3210
	12	66	65	4290
	31	130	30	3900

* Henderson and Lucas: Anesth. and Analg., 9, 1, 1930 (146).

ferent levels of anesthesia produced by cyclopropane, show that as a rule there was little change in the minute volume as the concentration of cyclopropane was increased, but that the tidal volume decreased, whereas the rate increased sufficiently to keep the minute volume near the control. Data from two experiments are presented in table 44.

In these two and fourteen other trained dogs, the amplitude of respiration (tidal air) was reduced markedly as the fourth plane of stage III anesthesia was reached.

TABLE 44

Effect of cyclopropane anesthesia upon the rate and minute volume of respiration

Dog	Cyclopropane, mgm per 100 cc Blood	Rate	Volume	Minute Volume
2	Control	16	200	3200
	11.5	14	200	2800
	18.5	27	125	3375
	20 8	32	120	3840
16	Control	34	130	4420
	16 5	21	160	3360
	19.5	25	110	2750
	26.2	25	120	3000

The rate of respiration in thirteen other dogs was found to be 31 per minute in the control, 47 per minute in stage III_2, 53 per minute in stage III_3, and 44 per minute in stage III_4.

In Monkeys

Shackell and Blumenthal (299) found a decrease in the rate of respiration in monkeys under cyclopropane anesthesia, and the decrease was more marked in the deeper planes as it is in man.

The evidence, both clinical and from the laboratory, shows that the respiration is not greatly altered by cyclopropane until the deeper planes of stage III are reached, and then the minute volume is decreased. The changes in respiratory rate of monkeys parallel the changes in man more closely than dogs and cats.

Tissue oxygenation, as indicated by studies of arterial and venous blood oxygen content, is adequate until the level of stage III_4 or respiratory arrest is reached.

In Man

Waters and Schmidt (341) have reported that there is no stimulation of respiration during induction or in the lighter planes of surgical anesthesia with cyclopropane. During the deeper planes there is a gradual diminution in the rate but a more marked reduction in the respiratory minute volume. There is no increase in rate with cyclopropane as there is with ether just prior to the development of respiratory arrest.

Waters (339) and Bourne (35) have reported that both the arterial oxygen and venous oxygen rise during anesthesia in man, with little or no change in the carbon dioxide content until respiratory depression is severe.

Stormont, Hathaway, Shideman, and Seevers (314) were the first to make studies upon the effect of cyclopropane anesthesia on the acid-base balance in man. They made careful studies on seventeen patients before and during anesthesia in relation to carbon dioxide tension of the alveoli, hydrogen ion concentration in the blood, the bicarbonate in the blood, and the effect of these

things upon the blood pressure. In their subjects, an oro-tracheal airway with a cuff was used and the to- and fro-carbon dioxide absorption technic was employed to remove the carbon dioxide from the expired air. The hydrogen ion content was increased in all subjects except one. The increase in hydrogen ion concentration varied from a change in the pH of 0.05 to 0.35 as a maximum. The change in carbon dioxide content varied from a decrease of 1 millimol per liter to an increase of 5.2 millimols per liter, with all but two cases showing an increase in the carbon dioxide content. The carbon dioxide tension was increased and a maximum change of 42.7 mm. of mercury was observed. The bicarbonates of the serum increased, the maximum being 4.2 millimols per liter. The arterial oxygen content on sixteen of these patients was determined, and fourteen of them showed an increase, the maximum increase being 2.2 volumes per cent. These observations substantiate those of Fay, Andersch, and Kenyon (99) and Robbins and Baxter (275) on dogs. They also determined the concentration of cyclopropane in the blood during these different experiments and found that this range was from 10 to 21 mgm. per 100 cc. in the thirteen patients in which it was determined. These values were obtained in patients during stage III, plane 1 to 3, surgical anesthesia and agree quite closely with those data obtained by Robbins, Baxter, and Fitzhugh (278) during the second and third plane of anesthesia in dogs. They found that the deeper the anesthesia the higher the level of carbon dioxide, and they felt as a result of this that in general there was a higher degree of acid-base displacement in those patients that had a higher concentration of the anesthetic agent. They observed, in a single patient, that by giving supplemental respiration relatively normal acid-base values could be maintained. Also, in thirteen patients there was an increase in the blood pressure of 25 mm. systolic and 17 mm. diastolic. They suggested in their summary that this shift in the acid-base value could be corrected by one of two mechanisms, either by eliminating the dead space in the mask and canister or by controlling artificially the rate and depth of

The rate of respiration in thirteen other dogs was found to be 31 per minute in the control, 47 per minute in stage III_2, 53 per minute in stage III_3, and 44 per minute in stage III_4.

In Monkeys

Shackell and Blumenthal (299) found a decrease in the rate of respiration in monkeys under cyclopropane anesthesia, and the decrease was more marked in the deeper planes as it is in man.

The evidence, both clinical and from the laboratory, shows that the respiration is not greatly altered by cyclopropane until the deeper planes of stage III are reached, and then the minute volume is decreased. The changes in respiratory rate of monkeys parallel the changes in man more closely than dogs and cats.

Tissue oxygenation, as indicated by studies of arterial and venous blood oxygen content, is adequate until the level of stage III_4 or respiratory arrest is reached.

In Man

Waters and Schmidt (341) have reported that there is no stimulation of respiration during induction or in the lighter planes of surgical anesthesia with cyclopropane. During the deeper planes there is a gradual diminution in the rate but a more marked reduction in the respiratory minute volume. There is no increase in rate with cyclopropane as there is with ether just prior to the development of respiratory arrest.

Waters (339) and Bourne (35) have reported that both the arterial oxygen and venous oxygen rise during anesthesia in man, with little or no change in the carbon dioxide content until respiratory depression is severe.

Stormont, Hathaway, Shideman, and Seevers (314) were the first to make studies upon the effect of cyclopropane anesthesia on the acid-base balance in man. They made careful studies on seventeen patients before and during anesthesia in relation to carbon dioxide tension of the alveoli, hydrogen ion concentration in the blood, the bicarbonate in the blood, and the effect of these

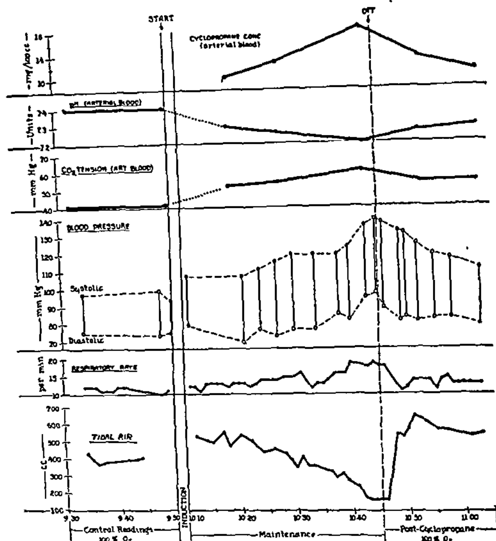


FIG 50 Effect of cyclopropane on pH and pCO_2 of arterial blood, on blood pressure, respiratory rate, and tidal air. The patient was a 29-year-old female, weighing 170 pounds; given morphine sulfate 10 mgm. and atropine sulfate 0 4 mgm at 8 45 A M (Dripps: Anesthesiology, 8, 15, 1947)

and the data on eleven patients in relation to changes of the blood pressure, the hydrogen ion concentration, and pCO_2 are given in table 45. It can readily be seen from figure 50 that there is an increase in the hydrogen ion concentration as the concentration of cyclopropane is increased during the anesthetic procedure,

respiration, thus preventing the general respiratory acidosis which occurs under cyclopropane-oxygen anesthesia, particularly in the deeper planes of anesthesia.

In 1947, Dripps (89) reported the results of his studies on the immediate decrease in blood pressure seen at the conclusion of cyclopropane anesthesia: "cyclopropane shock". This fall in blood pressure following the termination of cyclopropane anesthesia had been described clinically by others, but a satisfactory explanation of its etiology or cause had not been reported, so Dripps put two sets of data together and decided to make the study. The first set of observations used was the work by Stormont and his associates (314) who found that there were a marked respiratory acidosis during cyclopropane anesthesia and a simultaneous increase in both the systolic and diastolic pressure during cyclopropane anesthesia. The second set of experiments that came to Dripps' mind was the study by Goldstein and Dubois (111) who stated that at the sudden cessation of rebreathing there was a prompt decrease in blood pressure level. Comroe and Dripps (68) repeated work similar to Goldstein and Dubois and had a group of normal subjects breathe mixtures of air containing 7.8 or 10.4 per cent carbon dioxide With both mixtures there was an increase in the systolic blood pressure of approximately 30 mm. and in the diastolic pressure of approximately 20 mm. after eight and four minutes on the different concentrations. These concentrations of 7.8 and 10.4 per cent carbon dioxide in oxygen that were used by Dripps have been observed in the alveolar air in many subjects during cyclopropane anesthesia. In this study by Dripps, observations were made on patients in the controlled or awakened state, during the period of surgical anesthesia with cyclopropane, and for several minutes after the termination of the anesthetic and the operative procedure. Also obtained were the concentration of cyclopropane in the arterial blood, the pH of the arterial blood, carbon dioxide tension in the arterial blood, blood pressure, both systolic and diastolic, respiratory rate, and the tidal air. The typical results of the study on the patient are shown in figure 50,

15 to 8.4 mgm. or approximately 40 per cent. The tidal exchange was increased from 330 to 545 cc., an increase of approximately 60 per cent; the minute volume increase from 5.8 to 10.3 liters or approximately 95 per cent; and the pCO_2 of the arterial blood fell from 74 to 55 mm. of mercury on the way down to the control or normal level of 38 to 42 mm. of mercury. It is during this rapid shift of the pCO_2 that there is a fall in blood pressure at the termination of cyclopropane anesthesia, and this fall must be related in part to the artificially maintained high blood pressure as a result of increased CO_2 during cyclopropane anesthesia, as a result of diminution of tidal exchange and minute volume, and due to the rapid blowing off of carbon dioxide as a result of an increase of tidal air and minute volume immediately following the discontinuing of the administration of cyclopropane. Dripps feels, as a result of the depressant action of cyclopropane upon the respiratory mechanism in the human subject, that certain changes or particular points should be noted in relation to the preanesthetic medication and the maintenance of anesthesia with cyclopropane. First, he feels that morphine, a powerful respiratory depressant in its own action, should be reduced to a very small amount if employed. Second, that the events leading up to the postcyclopropane hypotension are the responsibility and fault of the anesthetist and not of the anesthetic—that is, the respiratory acidosis that ensues following unassisted respiration could be and should be prevented by adequate supplementation or control of respiration. Third, that during the later portion of the anesthesia, cyclopropane should be discontinued and nitrous oxide-oxygen introduced as the anesthetic agent during the final ten to fifteen minutes of a prolonged procedure. He feels that postoperative hypotension should be prevented through the maintenance of an adequate respiratory exchange during the anesthetic and operative procedure.

Bunker and his associates (45), in a continuation study of the metabolic effects of anesthesia in man and in dogs during ether and cyclopropane anesthesia, have made some very interesting

TABLE 45*

Effect of cyclopropane on pH and carbon dioxide tension (pCO_2) of arterial blood, and on arterial blood pressure

Data listed under "Mask On" were obtained three to five minutes before conclusion of anesthesia. The colum "Time" refers to the number of minutes elapsing between cessation of the closed system method of a demonstration and the collection of the blood sample. B.P. refers to the blood pressure at the time of the arterial puncture.

Patient	Normal B P.	Mask On				Mask Off			
		C_3H_6	pH	pCO_2	B P	B P.	pCO_2	pH	Time
		mg %		mm Hg			mm Hg		min
W P	128/62		6.99	120	200/80	100/60	73	7.12	16
E M	120/78	18	7 04	116	170/116	90/52	76	7.18	13
E F.	100/60	20	7 11	88	122/62	60/30	53	7.27	7
E S	140/90		7.10	84	140/90	62/40	48	7.24	14
E H	116/80	17.5	7 12	80	120/80	84/62	54	7.29	10
B.W.	125/78	19 2	7.16	76	140/80	80/55			12
R.B	100/65	18 1	7 20	64	140/96	112/80	54	7.28	17
L B	124/84	11.7	7.22	56	160/98	122/82	44	7.32	14
R P	115/65		7 29	55	112/70	87/60	45	7 35	3
S.B	110/70		7 32	48	102/70	100/70	42	7.38	7
E M.	110/80	5 5	7 37	42	120/88	130/90	42	7 38	4

* After Dripps Anesthesiology, 8, 15, 1947 (89).

that there is a simultaneous increase in the carbon dioxide tension of the arterial blood which parallels the rise in the blood pressure, there is an increase also in the respiratory rate, but a marked diminution in the tidal exchange during cyclopropane anesthesia. The rapidity with which there is a return to normal carbon dioxide tension in the blood and changes in the tidal air and minute ventilation following the termination of cyclopropane anesthesia can be noted in these data taken from a table of Dripps showing the decrease of cyclopropane, the increase in tidal exchange, the increase in minute volume and the decrease in the tension of the carbon dioxide in the arterial blood after the termination of the cyclopropane anesthesia has been made. In six subjects, these changes occurred in an average of seven minutes following the termination of the anesthetic. The cyclopropane was reduced from

15 to 8.4 mgm. or approximately 40 per cent. The tidal exchange was increased from 330 to 545 cc., an increase of approximately 60 per cent; the minute volume increase from 5.8 to 10.3 liters or approximately 95 per cent; and the pCO_2 of the arterial blood fell from 74 to 55 mm. of mercury on the way down to the control or normal level of 38 to 42 mm. of mercury. It is during this rapid shift of the pCO_2 that there is a fall in blood pressure at the termination of cyclopropane anesthesia, and this fall must be related in part to the artificially maintained high blood pressure as a result of increased CO_2 during cyclopropane anesthesia, as a result of diminution of tidal exchange and minute volume, and due to the rapid blowing off of carbon dioxide as a result of an increase of tidal air and minute volume immediately following the discontinuing of the administration of cyclopropane. Dripps feels, as a result of the depressant action of cyclopropane upon the respiratory mechanism in the human subject, that certain changes or particular points should be noted in relation to the preanesthetic medication and the maintenance of anesthesia with cyclopropane. First, he feels that morphine, a powerful respiratory depressant in its own action, should be reduced to a very small amount if employed. Second, that the events leading up to the postcyclopropane hypotension are the responsibility and fault of the anesthetist and not of the anesthetic—that is, the respiratory acidosis that ensues following unassisted respiration could be and should be prevented by adequate supplementation or control of respiration. Third, that during the later portion of the anesthesia, cyclopropane should be discontinued and nitrous oxide-oxygen introduced as the anesthetic agent during the final ten to fifteen minutes of a prolonged procedure. He feels that postoperative hypotension should be prevented through the maintenance of an adequate respiratory exchange during the anesthetic and operative procedure.

Bunker and his associates (45), in a continuation study of the metabolic effects of anesthesia in man and in dogs during ether and cyclopropane anesthesia, have made some very interesting

and careful observations on the changes or the constancy of the various values including the pH, serum carbon dioxide, hemoglobin, carbon dioxide tension, serum bicarbonate, and fixed acids. They found an increase in fixed acids of 1.8 millimols per liter which is not significant. There was an increase in the carbon dioxide tension of 8 mm. of mercury, indicating a slight respiratory acidosis which he maintains can be corrected by adequately controlled respiration or adequate assistance to the respiration. Likewise, in the series of dogs they studied, there was no significant alteration in the fixed acids, but there was an increase in carbon dioxide tension from 34.8 to 41.7 mm. of mercury.

In 1953, Buckley and his associates (43) reported their study on the postanesthetic hypotension following cyclopropane anesthesia and its relation to hypercapnia. They made a continuous analysis of the alveolar carbon dioxide concentration by use of the mass spectrometer. They studied the changes in fifteen patients under cyclopropane anesthesia without assisted respiration and sixteen patients with assisted respiration and correlated the changes in the alveolar CO_2 content with that of the blood pressure during the operative procedure and for a considerable time following the anesthetic. Typical examples of their studies are shown in figure 51 in which the subject was unassisted, and one observes a rise in the alveolar CO_2 tension, a marked rise in the systolic pressure of the patient, with a very rapid fall of the CO_2 tension and the arterial blood pressure after the termination of the administration of the anesthetic. Figure 52 shows the results of a patient in whom the respiration was assisted, and one notes that the alveolar CO_2 tension was held at a relatively constant level, with the blood pressure being relatively normal during this anesthetic period, and the absence of marked fall at the termination of the anesthetic period. In this series of patients with unassisted respiration, the alveolar carbon dioxide content reached a level of 12.3 per cent on the average, whereas in the group that had manually assisted respiration the highest CO_2 content attained was 6.8 per cent. They conclude that cyclopropane shock is a result of inadequate respiratory minute volume resulting in

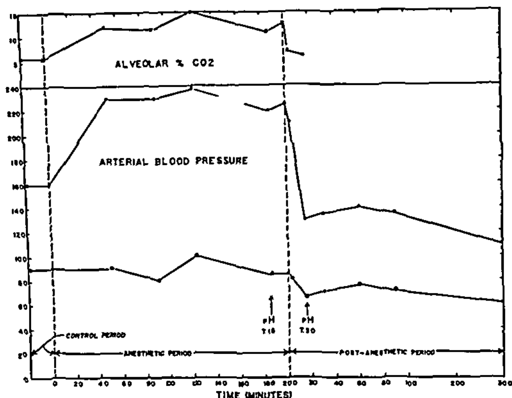


FIG. 51. Chart on patient D.S , age 33, illustrating the rapid development of hypercapnia during light cyclopropane anesthesia when respiration is not augmented. Observe the profound hypotension in the early minutes of the post-anesthetic period (Buckley *et al.*· Anesthesiology, 14, 226, 1953)

the accumulation of carbon dioxide during the anesthesia and its rapid diminution at the termination of the anesthetic period, and that this can be prevented by the maintenance of normal alveolar carbon dioxide tension by manually augmenting the respiration during the anesthetic period.

EFFECT OF PREMEDICATION UPON RESPIRATION

Waters and Schmidt (341) stated that since cyclopropane did not increase respiration, the premedication should be reduced in amount. They believe that better results were obtained with morphine and scopolamine and have not used barbiturates with cyclopropane.

Experimental studies by Robbins, Fitzhugh, and Baxter (278)

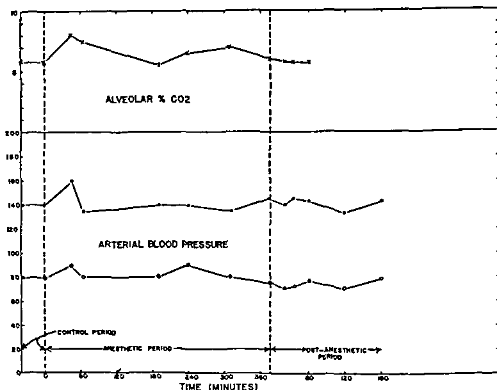


Fig. 52 Chart on patient J.S , age 42, cyclopropane anesthesia Alveolar carbon dioxide level was maintained within the normal range by manual assistance to respiration Note that the blood pressure remained unaltered in the post-anesthetic period. (Buckley *et al.*· Anesthesiology, **14**, 226, 1953)

upon dogs with morphine, barbital, or amytal as preanesthetic medication failed to show any significant differences in the carbon dioxide content of the arterial blood in the three groups of dogs during deep anesthesia and at respiratory arrest; the oxygen content of the blood in the dogs receiving barbiturates was about the same as the morphine group during stage III_{3-4} anesthesia, but was 3 to 4 volumes per cent higher at respiratory arrest than that in the morphine and control groups. Data on blood gas changes in thirty-seven dogs with and without premedication are shown in table 32.

From these data we feel that barbiturates, even in amounts that are relatively much larger than the morphine, do not reduce the adequacy of respiration as much as morphine.

EFFECT OF HIGH OXYGEN CONTENT OF THE ANESTHETIC MIXTURE UPON RESPIRATION

The high oxygen tension in the anesthetic mixture is an important factor in determining the rate and amplitude of respiration in animals and probably in man.

In their studies on monkeys, Shackell and Blumenthal (299) found that with an average of 70 per cent oxygen in the anesthetic mixture the concentration of cyclopropane necessary to produce respiratory arrest was only 25.7 per cent, whereas when the oxygen content was about the same as that in air (20 per cent), a concentration of 33.7 per cent cyclopropane was necessary to produce respiratory arrest. Data from their experiments are given in table 46.

In the light of other data to be discussed below, there is little doubt but that the high concentration of oxygen in the anesthetic mixture is the main factor in reducing the amount of cyclopropane necessary to produce respiratory arrest in the monkeys.

It is of interest here to speculate whether or not such factors hold true in man. Data similar to those of Shackell and Blumenthal are presented in figure 5 from Waters and Schmidt, where it is shown that in the patient which developed respiratory arrest with the lowest concentration of cyclopropane—26.2 per cent—there was an oxygen content of 56 volumes per cent, whereas in

TABLE 46*

Effect of oxygen upon the concentration of cyclopropane for respiratory arrest in monkeys

Number of Observations	Oxygen Concentration	Cyclopropane
5	20.2	33.7
5	28.7	34.0
5	37 4	36.4
5	46.4	30.9
5	55.1	29.4
3	70.5	25.7

* Shackell and Blumenthal· Anesth. and Analg., 13, 133, 1934 (299).

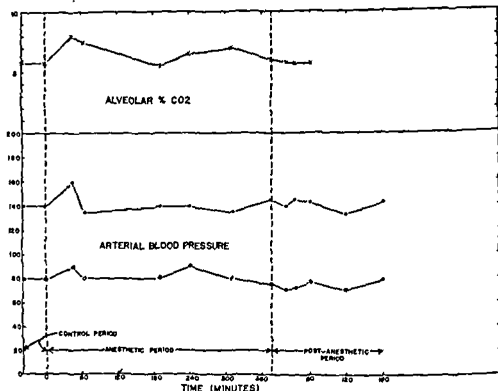


FIG. 52 Chart on patient J.S, age 42, cyclopropane anesthesia Alveolar carbon dioxide level was maintained within the normal range by manual assistance to respiration Note that the blood pressure remained unaltered in the post-anesthetic period (Buckley *et al* · Anesthesiology, 14, 226, 1953)

upon dogs with morphine, barbital, or amytal as preanesthetic medication failed to show any significant differences in the carbon dioxide content of the arterial blood in the three groups of dogs during deep anesthesia and at respiratory arrest; the oxygen content of the blood in the dogs receiving barbiturates was about the same as the morphine group during stage III_{3-4} anesthesia, but was 3 to 4 volumes per cent higher at respiratory arrest than that in the morphine and control groups. Data on blood gas changes in thirty-seven dogs with and without premedication are shown in table 32.

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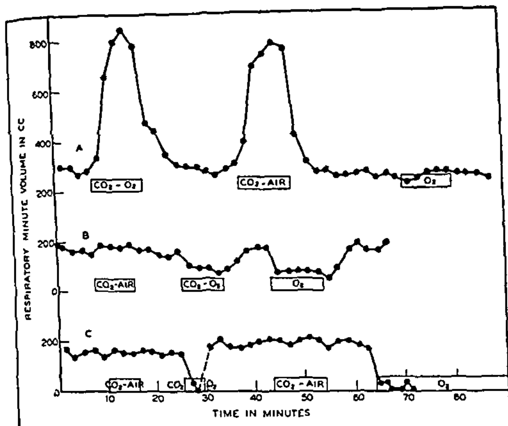


FIG 53 Upper curve A gives responses to 7 per cent carbon dioxide in oxygen and in air, and to pure oxygen of a cat given 195 mgm per kilogram of phenobarbital sodium. Middle curve B after injection of 1 mgm. per kilogram morphine sulfate. Lower curve C after additional injection of 2 mgm. per kilogram of morphine sulfate together with 15 mgm per kilogram phenobarbital sodium (After Marshall and Rosenfeld. J Pharmacol & Exper. Therap , 57, 437, 1936)

excess increased the rate in eight of twenty-four experiments. In another study, Rosenfeld and Snyder (285), using rabbits at term in which labor had been inhibited by the injection of antuitrin-S one week before term, have investigated the effects of pentobarbital, morphine, paraldehyde, and chloral hydrate, as well as ether, nitrous oxide, and cyclopropane, upon the fetal respiration. All of the basal narcotics abolished the fetal respiration for several minutes although the mother was in no case anesthetized. With ether the fetal respiratory activity was stopped during the time

the patient which required the highest concentration of cyclopropane—49.7 per cent—to produce respiratory arrest, the concentration of oxygen was 35.5 per cent. It is probable that such correlation is only fortuitous; nevertheless it is interesting.

The data of Shackell and Blumenthal on the effect of oxygen tension upon the concentration of cyclopropane necessary to produce respiratory arrest are in substantial agreement with the observations of Marshall and Rosenfeld (199), who found that the administration of high concentrations of oxygen to animals under certain anesthetics, particularly the barbiturates and barbiturates plus morphine, produced a marked depression of respiratory minute volume. A chart taken from the report of Marshall and Rosenfeld is given (fig. 53).

The most plausible explanation of the action of high tension of oxygen in further depressing respiration and producing apnea in animals with the respiratory mechanism already depressed by by anesthetics is that of Marshall and Rosenfeld (199) and Schmidt (293), who feel that in the depressed animal respiration is maintained by the stimulant action of relative anoxia upon the sino-aortic mechanism (carotid bodies and aortic bodies), and that when high concentrations of oxygen are given, this anoxic stimulus is abolished and respiration is further decreased or apnea develops.

RELATION OF ANESTHESIA AND PREMEDICATION TO ASPHYXIA OF THE NEWBORN

The effects of anesthetics and premedication agents in relation to asphyxia of the newborn have been studied in some detail. Snyder and Rosenfeld have shown in the experimental animal (308), as well as in man (307), that the normal fetus has active respiratory movements with aspiration and expulsion of amniotic fluid for some time before term or delivery. They have investigated the effects of anoxia, excess carbon dioxide, and acapnia upon the fetal respiration and found that anoxia and acapnia depressed the rate of respiration in all experiments, whereas carbon dioxide

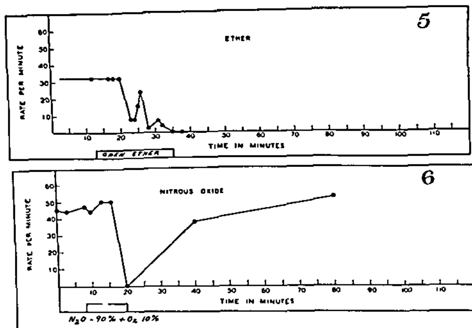


Fig. 54. 5—Ether by drop method. Gradual depression of fetal respiration which persisted in this instance after mother awakened from anesthesia. 6—Nitrous oxide, 90 per cent; oxygen, 10 per cent. Mother depressed, corneal reflex present. (Rosenfeld and Snyder· Am J Obst. & Gynec., **38**, 425, 1939)

anesthesia which has, according to Burford, a purely physical basis, due to the rapid rate of absorption of both cyclopropane and oxygen from the alveoli.

Burford (47) maintains that at the end of a period of anesthesia with cyclopropane-oxygen, the mixture in the patient's alveoli and in the bag is practically pure cyclopropane and oxygen with only a minimal amount of inert gas; this is due to the fact that as anesthesia proceeds, there is an escape of gas from the anesthetic system, which is in turn replaced with cyclopropane-oxygen, so that most of the nitrogen which was originally in the lungs has been lost. During the deeper levels of anesthesia the respiratory volume is decreased, and the distal alveoli are not dilated with each inspiratory effort, so there is a rapid absorption of cyclopropane and oxygen and the alveoli collapse. While the anesthetic mixture, high in oxygen, is being given, there is adequate oxygenation of the blood, even with partial collapse of the alveoli, and the

TABLE 47*

Effect of anesthetics upon fetal respiration (rabbit)

Anesthetic	Approximate	Number of Animals	Number of Fetuses	Surgical Anesthesia of Mother	Suppression of Intrauterine Respiration of Fetus
	mgm per kgm				
Pentobarbital-Na	20	9	27	0	+
Morphine-SO_4	5	4	16	0	+
Paraldehyde	250	3	5	0	+
Chloral hydrate	25	2	15	0	+
Ether, open-drop technic		3	8	0	+
Nitrous oxide 90%-oxygen 10%		3	10	0	+
Nitrous oxide 85%-oxygen 15%		4	15	0	0
Cyclopropane 30%-oxygen 70%		9	32	+	0

* Rosenfeld and Snyder. Am. J Obst and Gynec., **38**, 425, 1939 (285).

the mother was anesthetized, nitrous oxide, 90 per cent, and oxygen, 10 per cent, mixtures abolished fetal respiration even though the mother was not anesthetized; nitrous oxide, 85 per cent, and oxygen, 15 per cent, did not depress the fetal respiration. Only with cyclopropane-oxygen were they able to produce surgical anesthesia in the mother without depressing or abolishing fetal respiration.

In summarizing their report they state, "most anesthetics of both nonvolatile and volatile types suppress intrauterine respiration long before surgical anesthesia is reached in the mother. The result with cyclopropane illustrates the attainment of one important objective in obstetric anesthesia, namely, the production of full surgical anesthesia of the mother without interruption of fetal respiration."

Table 47 and figures 54 and 55 are taken from their paper and show in detail their results.

RATE OF ABSORPTION OF GASES IN RELATION TO POSTOPERATIVE ATELECTASIS

Jones and Burford (162) have reported cases of pulmonary collapse or massive atelectasis following cyclopropane-oxygen

TABLE 48*

Time necessary for the absorption of fixed amounts of different gases

Gas Used	Number of Experiments	Average Time for Absorption	
		minutes	*seconds*
CO_2	9	1	16
O_2	12	1	20
N_2O	6	1	42
C_2H_4	3	2	2
H_2	3	16	22
Argon	3	16	4
Helium	1	18	16
Air	12	9	22
N_2	6	12	6

* Lemmer and Rovenstine: Arch. Surg., *30*, 625, 1935 (182).

Coryllos and Birnbaum (70), in their studies on the rate of absorption of different gaseous agents, obtained some very interesting data. After having rendered a lobe of the lung atelectatic, by flushing it out six to eight times with oxygen and allowing the oxygen to be absorbed while the bronchus was obstructed, they inflated the lobe with the gas to be studied, then closed the bronchus and observed the time necessary for complete absorption. Their results show a wide variation in the rate of absorption as estimated by the time necessary for the gas to be absorbed. The time required for the different agents is: oxygen, 15 minutes; carbon dioxide, 4 minutes; N_2O, 17 to 35 minutes; C_2H_4, 13 to 29 minutes; ether vapor, 1 to 3 minutes; ethyl chloride vapor, 10 to 17 minutes; air, 16 hours; N_2, 16 hours; hydrogen, 18 hours; and helium, 26 hours.

Later Lemmer and Rovenstine (182) used as a measure of the rate of absorption the time necessary for the absorption of 600 cc. of the different agents from one lung that had been previously allowed to collapse, following obstruction of the bronchus, and then inflated with the gas under study. They determined the time necessary for the lung to diminish to one-sixth of the inflated size

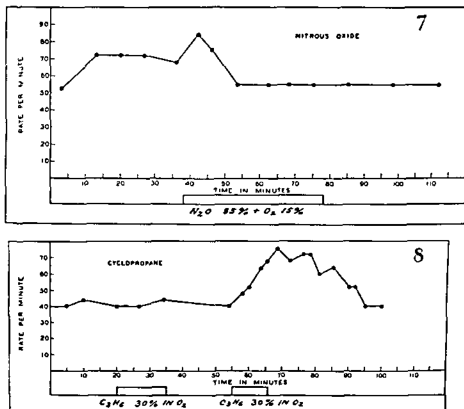


FIG 55 7—Nitrous oxide, 85 per cent; oxygen, 15 per cent Mother awake, reflexes active 8—Cyclopropane, 30 per cent; oxygen, 70 per cent. Mother fully anesthetized, corneal reflex lost Deep surgical anesthesia of mother without interruption of fetal breathing (Rosenfeld and Snyder. Am. J. Obst. & Gynec., **38**, 425, 1939)

patient remains pink and in good condition. With sudden withdrawal of the anesthetic mixture while the patient is still anesthetized, the oxygen and cyclopropane in the alveoli are absorbed rapidly and more alveoli collapse, even though there is no obstruction present; atelectasis follows because there is no inert or unabsorbable gas present. Burford advises the use of some inert gas in the anesthetic mixture so that the distal alveoli will not collapse during anesthesia or soon after, due to complete absorption of the oxygen and cyclopropane while the respiration is still reduced below normal.

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and determined this time for several agents. Data from their results are shown in table 48.

On the basis of their results, they advise that if CO_2 is to be given after anesthesia to prevent postoperative atelectasis, it should be given in an atmosphere of air and not of oxygen because of the slower rate of absorption of air in an obstructed or partially obstructed lung area.

To aid in the prevention of postoperative pulmonary collapse following inhalation anesthesia, Burford suggests that some inert, slowly absorbed gas be added to the anesthetic mixture. This can be done when one uses cyclopropane because it is the only one of the gaseous agents of sufficient potency to permit adequate oxygen tension and 30 to 40 per cent of an inert agent. Burford has used helium in his cases.

SUMMARY

Cyclopropane does not irritate the upper respiratory tract as much as chloroform or ether.

Although respiration is not increased during cyclopropane anesthesia, tissue oxygenation is adequate. The high concentration of oxygen used with cyclopropane is a factor in the reduced respiratory activity during anesthesia.

Cyclopropane does not stimulate respiration, and unless the respiratory effort is augmented, a respiratory acidosis will develop.

The absence of slowly absorbed gases in the alveoli at the end of the anesthetic period may be a factor in the development of atelectasis following cyclopropane-oxygen anesthesia.

5

The Effects of Cyclopropane Anesthesia Upon The Gastrointestinal Tract

From the literature relating to the postoperative complications of the gastrointestinal tract following anesthesia, it is concluded that distention and ileus are less frequently observed after cyclopropane than ether anesthesia. This would indicate that cyclopropane has less effect on normal gastrointestinal tone and activity than the ether.

Experimental studies of the effects of cyclopropane upon the tone and contraction of intestinal muscle have been made in vitro as well as in vivo in dogs and man.

Peoples and Phatak (252) used the Magnus method of studying the effect of cyclopropane upon the tone and contraction of 2 cm. segments from the jejunum of rabbits. By bubbling 10 to 25 per cent mixture of cyclopropane through the bath, they found that the tone of the muscle strip was increased but the amplitude of contractions was decreased. These results of excised rabbit tissue were confirmed by Beyer (quoted by Weisel, Youmans, and Cassels (342)). Upon placing the tissue in fresh Locke's solution the tone and contraction rapidly returned to normal. Ether, on the other hand, decreases both tone and contraction. A record of their results is shown in figure 56.

Burstein (51) studied the effects of anesthesia on tone and contraction in six dogs with chronic Thiry-Vella fistulae in the jejunum or ileum. Intestinal movements were recorded by using a balloon in the gut connected to a water manometer as described by Jackson (155). The dogs were not given any premedication. After control records were made, anesthesia was induced and an



Fig. 56. Effect of 10 per cent cyclopropane in oxygen on intestinal muscle (After Peoples and Phatak Proc Soc Exper. Biol & Med., 33, 287, 1935)

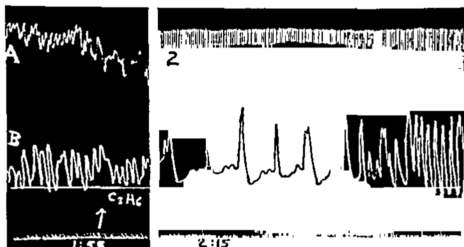


Fig 57. Effect of cyclopropane on intestinal activity in dog with Thiry-Vella fistula of the jejunum Upper curves (A) thoracic respirations, lower curves (B) intestinal contractions (After Burstein. Proc. Soc Exper Biol & Med, 38, 530, 1938)

endotracheal airway inserted, after which anesthesia was maintained by a closed system with a CO_2 absorber in line.

The amplitude of contractions as well as the tone was increased in stage III_{1-2} ; in stage III_3 the tone remained high but the amplitude of contractions was decreased; in stage III_4 the amplitude of contractions was markedly reduced but the elevation of tone persisted. Upon reducing the depth of anesthesia, the contractions increased. A record of Burstein's results is shown in figure 57.

He also confirmed the earlier work of Miller (212) in finding

TABLE 49*

Effect of bolus propulsion time of cyclopropane alone and of cyclopropane after morphine and scopolamine premedication

Propulsion times are recorded in minutes and are consecutive horizontally except in the four instances where an interval was allowed to pass after the last time recorded for the premedicated intestine before the beginning of cyclopropane anesthesia.

Dog Number	Normal Propulsion Times							Length of Anesthesia	Propulsion Times Immediately Following Beginning of Cyclopropane Anesthesia							
1	5	5	3					41	46	2	160	165	160	4	6	
2	4	4	4					30	35	6	6	7	3	4		
3	10	8	8					34	48	49	10	9	88			
4	10	9	9					26	28	13	9					
5	8	4	4					16	33	3	9	4				
6	3	3	3					34	99	15	8	5	3			
7	14	14	15					22	28	8	14	14				
	Normal Propulsion Times			Propulsion after Morphine Scopolamine			Interval	Length of Anesthesia	Propusion Times Immediately Following Beginning of Cyclopropane Anesthesia							
1	5	4	4	2	2	20		30	40	7	6	4				
2	3	3	3	1	1	18		44	33	12	3	1	8	1	1	1
3	13	8	8	2	2	3	31	51	116	4	2	2				
4	15	9	8	2	3	4	28	45	48	3	3	25	9	8	8	
5	5	6	5	1	1	2		21	27	65	4	9				
6	15	8	8	3	2	4	6	15	19	4	3	4	4	30	102	8
7	14	14	14		4	33	25	30	53	8	35	47	21	14		

* After Weisel, Youmans, and Cassels. J. Pharmacol and Exper Therap., 63, 391, 1938 (342).

that under ether anesthesia the intestinal activity was decreased.

Weisel, Youmans, and Cassels (342) have made a very complete study on the effect on intestinal motility of cyclopropane anesthesia alone and after morphine-scopolamine premedication. They studied the effects on tone, propulsive and non-propulsive movements in dogs. Eleven dogs were used; some had a normal Thiry fistula, denervated Thiry fistula; others had a normal Thiry-Vella fistula; while two had both Thiry and Thiry-Vella fistulae.

They first investigated the effects of morphine and scopolamine alone and combined upon tone, propulsive and non-propulsive movements, and later the effect of cyclopropane anesthesia on these factors in non-premedicated and premedicated dogs. They used morphine, 1 mgm. per kilogram subcutaneously, and scopola-

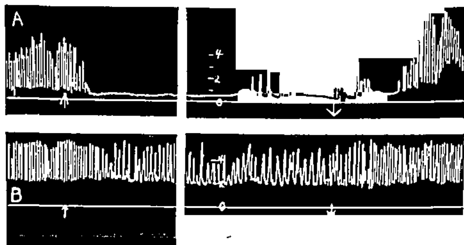


Fig. 58 A Typical effect of cyclopropane anesthesia (between arrows) on the motility of a jejunal fistula of a non-premedicated dog A 12-minute section of record was removed at the break Artificial respiration during minute following end of anesthesia

B. Effect of cyclopropane anesthesia (between arrows) 25 minutes after injection of morphine and scopolamine A 20-minute section of record was removed at the break

Time in 5 seconds and 1-minute intervals Pressure in centimeters of mercury (After Weisel, Youmans, and Cassels J Pharmacol. & Exper. Therap., 63, 391, 1938)

mine, .6 to 1.2 mgm. total dose subcutaneously. Anesthesia was given by the closed CO_2 absorption technic, and records were made under different levels of anesthesia.

It was found that scopolamine alone decreased markedly the bolus propulsion action for about two hours; with morphine alone and morphine with scopolamine the propulsive action was increased for a few minutes following the injection but was later decreased. The effects of cyclopropane anesthesia upon the propulsive action in normal and premedicated dogs are shown in table 49.

During the periods of anesthesia in the different dogs, only one (no. 2) with premedication expelled the bolus before the anesthesia was stopped. The propulsive activity of the gut then is practically abolished during surgical anesthesia with cyclopropane.

In the non-premedicated dog the contractions were abolished

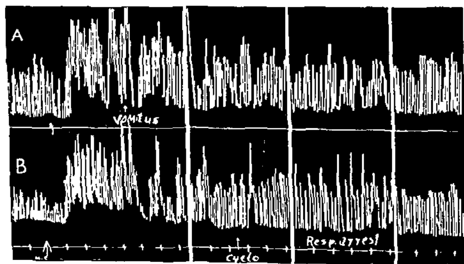


FIG 59 Effect of morphine and scopolamine (1st arrow) followed by cyclopropane anesthesia (2nd arrow) on an innervated (A) and a denervated (B) jejunal fistula Twenty, 10 and 10-minute sections have been removed at the 1st, 2nd and 3rd breaks, respectively Anesthesia was ended 3 minutes preceding the last section Time in minutes (After Weisel, Youmans, and Cassels: J Pharmacol & Exper. Therap., 63, 391, 1938)

during anesthesia, but the tone was not altered, whereas in the premedicated dogs the frequency of contractions was reduced during anesthesia without much change in the amplitude or tone. Records are given in figure 58.

The effect of morphine-scopolamine in maintaining the contractions (non-propulsive) during anesthesia with cyclopropane is not dependent upon any central nervous mechanism because practically identical records are obtained from innervated and denervated jejunal fistula. An excellent comparison is shown in figure 59.

Seevers (295) found that the inhalation of cyclopropane in six per cent concentration for ten minutes inhibited hunger contractions in man, but the gastric tone was not changed. The contractions returned in full strength when inhalation ceased and progressed to the usual tetanic contracture.

Bisgard and Johnson (23, 24) reported that anesthesia produced with cyclopropane combined with avertin was followed by less postoperative disturbances than observed in patients following anesthesia by other agents. They showed in both man and dog that the tone and contractility of the gastrointestinal tract were changed less under cyclopropane alone and combined with avertin than when ether, nitrous oxide, or evipal was used. They suggest that the reduction in gastrointestinal activity may be due to anoxia because the activity is increased during the inhalation of oxygen.

SUMMARY

Cyclopropane increases the tone of intestinal muscle in vitro.

Cyclopropane anesthesia alone reduces the frequency of or abolishes the contractions of the intestine of dogs.

Cyclopropane when given after morphine and scopolamine abolishes the propulsive action of the gut but does not alter the amplitude of the segmented or non-propulsive contractions in the dog.

6

The Effects of Cyclopropane Anesthesia Upon the Blood

Relatively few studies have been reported upon the changes in the blood during cyclopropane anesthesia, but there is fair agreement in the data obtained by different workers.

Henderson and Lucas (146, 147) found very little change in the pH of the blood during periods of anesthesia from one to two hours' duration in eight experiments in cats and rabbits; the pH increased about as often as it decreased as the anesthesia continued; they did not do control pH determinations.

Fay, Andersch, and Kenyon (98, 99) have reported a comparative study on the serum electrolyte changes under ether and cyclopropane anesthesia in dogs; they found in six of fourteen determinations of pH under cyclopropane no significant change (pH $\pm$.05 or less) from the control value, while in the other eight there was a fall of .06 to .27 pH. Ether produced a fall of .06 to .3 pH in all of ten determinations.

There is little change in the carbon dioxide content of the blood produced by cyclopropane anesthesia until the lower planes of stage III are reached. Hathaway and Orcutt (quoted by Waters (339)) found an increase in both arterial and venous carbon dioxide in patients with premedication; Robbins and Baxter (277), in studies on non-premedicated dogs, found little change in the carbon dioxide content until the time of respiratory arrest; in dogs with morphine or barbiturate premedication there was an increase of 4 to 10 volumes per cent, depending upon the size dose of preanesthetic medication. See table 32, Chapter 3, for detailed data. Fay, Andersch, and Kenyon reported that they found no consistent change in the carbon dioxide content.

The oxygen content of arterial and venous blood rises during anesthesia, and the arterial-venous oxygen difference is decreased. Hathaway and Orcutt found this in man; Robbins and Baxter obtained similar results in non-premedicated dogs. The arterial oxygen content also rises in premedicated dogs during anesthesia and is higher at respiratory arrest in the barbiturate premedicated dogs than in the control or morphine premedicated dogs. Fay, Andersch, and Kenyon (99) also found an increase in oxygen content during anesthesia.

Waters and Schmidt (341) reported that there is no significant change in the carbon dioxide combining power immediately and four hours after cyclopropane anesthesia on twenty-one patients. Fay, Andersch, and Kenyon (99) found a slight rise in three dogs, a slight fall in two, and 8.49 volumes per cent fall in another dog under cyclopropane anesthesia, whereas with open-drop ether anesthesia they found a fall of 10 to 15 volumes per cent in five experiments, with ether in the closed system there was an average fall of 4.7 volumes per cent in eleven experiments. Neff and Stiles (229) reported a fall in carbon dioxide combining power of 2 to 7 volumes per cent in twenty-five patients; they found no significant change in the combining power in thirty controlled diabetics after cyclopropane anesthesia (see table 50 for their results).

TABLE 50*

The effect of anesthesia upon the blood sugar and carbon dioxide combining power of the plasma of diabetic patients

Agent	Time	Blood Sugar	Carbon Dioxide Combining Plasma	Duration of Anesthesia	Number of Patients
		mgm per cent		*minutes*	
Nitrous oxide	Preoperative	196	56 4	17	30
	Postoperative	200	52.7		
Spinal procaine	Preoperative	194 4	54.7	31	30
	Postoperative	195 1	51 9		
Cyclopropane	Preoperative	175	54.9	31	30
	Postoperative	181 9	53.2		

* Neff and Stiles Canad M A J, 35, 56, 1936 (229).

Fay, Andersch, and Kenyon (99) reported that the total base may remain constant or rise with cyclopropane, whereas there is a fall with ether; in this relation it is interesting to note that with both cyclopropane and ether there is a fall in sodium, but potassium which always falls with ether, as shown by Cloetta *et al.* (61) and Robbins and Pratt (281), may or may not change under cyclopropane.

Waters and Schmidt (341) reported an increase in inorganic phosphorus during cyclopropane anesthesia in man. Fay, Andersch, and Kenyon (99) found similar changes in the dog; ether, when given by the closed system, increases the phosphate, but open-drop ether produces a fall.

There is no significant change in the NPN in man after cyclopropane anesthesia as reported by Waters and Schmidt (341) and Neff and Stiles (229).

In rabbits and cats Henderson and Lucas (146, 147) found no change in blood sugar in two experiments, whereas in three others there were increases of 38 to 86 mgm., but their remarks would indicate that factors other than the anesthetic were operating to produce the increase.

Waters and Schmidt (341) reported a 10 to 15 per cent rise in blood sugar immediately after anesthesia with a return to the preanesthetic level in four hours. Whether this slight rise is due to the cyclopropane or the morphine premedication cannot be stated with certainty because morphine produces a rise in blood sugar in man and lower animals. Bodo *et al.* (27), using relatively small doses of morphine in dogs, found rises in blood sugar of some 10 to 15 per cent.

In controlled diabetics having intra- and extra-abdominal surgery, Neff and Stiles (229) compared the blood chemical changes in thirty patients in each group with nitrous oxide, spinal, and cyclopropane anesthesia. The preoperative blood samples were taken three hours before operation; the calculated doses of insulin and glucose for each patient were given immediately after the preoperative samples were taken. The postoperative samples were

taken four hours after the operation and before any insulin or glucose was given. Their results are shown in table 50.

In the controlled diabetic, cyclopropane anesthesia does not alter the blood sugar or carbon dioxide combining power.

Taylor and Waters (327) have made a study of the effects of various anesthetics upon the white blood corpuscle count in patients and found that there was a marked increase during the eight hours following anesthesia, with a rapid return toward normal in twenty-five hours, with a more gradual return to normal during the third to fifth postoperative days. Figures from their report are given in figures 60 and 61.

The longer the duration of the anesthesia, the higher the leucocytosis. In similar operations under local (procaine), ether, or cyclopropane the rise in wbc is much greater with ether or cyclopropane than with the local. The rise is greater in intra-abdominal than in extra-abdominal cases. These data were taken from pa-

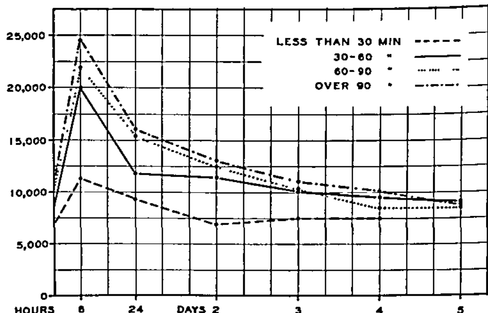


FIG 60 Postoperative leucocytosis according to operating time in all cases. Cases done in less than thirty minutes had superficial operations. The remainder that are separated into three time groups had similar operations that varied in respect to duration (After Taylor and Waters: Anesth. & Analg, 14, 277, 1935)

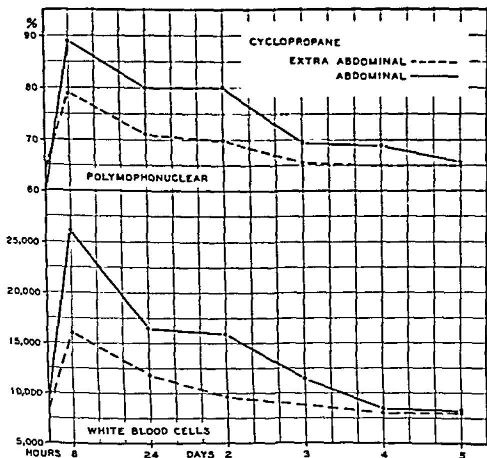


FIG. 61. Percentages of polymorphonuclear cells in thirty-six cases anesthetized with cyclopropane The cases are separated into abdominal and extra-abdominal surgery.

Leucocytosis in thirty six cases anesthetized with cyclopropane. The cases are separated into abdominal and extra-abdominal surgery. (After Taylor and Waters: Anesth & Analg, 14, 277, 1935)

tients without diagnosed infective processes, so it seems that the anesthetic, per se, produces leucocytosis. To confirm this point they made studies on five dogs which were anesthetized to levels of deep anesthesia with ether for periods of one to one and one-half hours. Cell counts made three hours after the anesthesia showed two and one-half times the control wbc value, whereas at twenty-four hours the count was only about 25 per cent above the control, and at forty-eight hours the count was normal.

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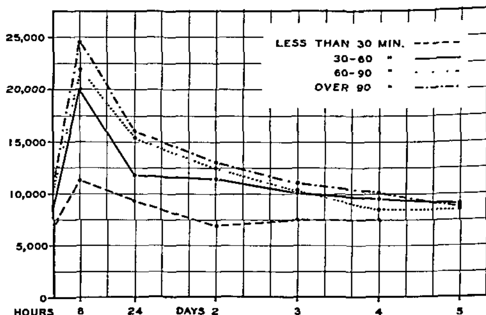


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7

The Effects of Cyclopropane Anesthesia Upon Other Tissue

Cyclopropane does not increase the secretion of saliva as much as ether or chloroform (271) although Marshall (200) states that cyclopropane stimulates the parasympathetic system, because he found an increase of lachrymal and salivary secretion along with a contraction of the iris, the gut, and a bradycardia.

There are no data to show the effect of cyclopropane upon the secretion from the glands of the gastrointestinal tract.

Raginsky and Bourne (262) and Bourne (34) have made studies upon the effect of cyclopropane on the liver as determined by the bromsulphthalein liver function test. Tests were made on three normal women before and after cyclopropane anesthesia, and there was no reduction of rate of removal of the dye from the blood stream; in one patient with eclampsia who had a retention of 55 per cent before cyclopropane and delivery, there was a retention of 50 per cent after anesthesia and delivery.

They made studies upon the effect of repeated cyclopropane anesthesia in normal dogs and in dogs after liver injury due to $CHCl_3$ poisoning. One dog that was anesthetized one hour daily for nine days showed a 10 per cent retention after the first and third day, but none after the other. Histological examination of the liver from this dog showed no changes similar to those produced routinely with $CHCl_3$ and occasionally with ether. In the dogs with damaged livers due to $CHCl_3$ poisoning anesthetization with cyclopropane for long periods (three hours) did not alter the rate of recovery.

These data both clinical and laboratory indicate that cyclopropane anesthesia does not produce damage to the normal liver

Garrey and Butler, quoted by Garrey and Bryan (106), found that anesthesia in dogs, produced by barbiturates, was not accompanied by leucocytosis and that subsequent inhalation of ether did not produce a leucocytosis. They suggested that part of the leucocytosis during and following ether anesthesia might be due to emotional and reflex reactions and struggle during induction.

Mann (193) believes that the leucocytosis after anesthesia is due to the stimulant action of the anesthetic upon the bone marrow and not to the expulsion of wbc from the spleen and other wbc depots.

Taylor and Waters found no changes in the rbc in eight cases after anesthesia. Fay, Andersch, and Kenyon (99) in their studies on dogs found that the cell volume increased an average of 4.3 volumes per cent. Robbins, Baxter, and Fitzhugh (279) reported an increase in the oxygen capacity in dogs under cyclopropane after premedication with barbiturates.

There is no change in the clotting time under cyclopropane anesthesia (327).

SUMMARY

Cyclopropane anesthesia produces no significant change in the pH, carbon dioxide content, or carbon dioxide combining power of the blood.

The oxygen content and capacity are increased during anesthesia.

Total bases of the serum are not changed.

Inorganic phosphates are increased after cyclopropane anesthesia.

The non-protein nitrogen is not increased after cyclopropane anesthesia.

The blood sugar rises slightly in normal patients, but there is no change in controlled diabetics.

There is a marked leucocytosis following cyclopropane anesthesia, but only slight changes in the red cells.

urine output, creatinine clearance, and para-aminohippurate clearance. There was a reduction in these three values of approximately 50 per cent during this deep anesthesia. Immediately following the deep anesthesia the dogs were again lightened to stage III, plane 1, anesthesia and studies on urinary function repeated. The creatinine clearance, urine output, and the para-aminohippurate clearance were approximately the same as they were in the control studies. They feel that there is a reduction in blood flow of about one-half during deep anesthesia and that this is due to neurogenic constriction of the vessels.

In 1952, Miles and DeWardener (211) reported their study on the renal vasoconstriction produced by ether and cyclopropane anesthesia. This was done on dogs that had the kidney in normal position and also the kidney that had been denervated. They observed marked vasoconstriction during anesthesia with cyclopropane and ether and found that when the kidney was denervated, ether produced a vasoldilatation. They believed that the reduction in blood flow through the kidney is due to neurogenic vasoconstriction of the vessels in the kidney.

In 1943, Collier and his associates (64) reported a study on the effect of ether and cyclopropane anesthesia on the renal function in man. They made control studies of the patient in the awakened state, and their experimental observations were near the end of or immediately following the operative procedure. They studied seven patients with ether and four with cyclopropane. They determined the glomerular filtration by the inulin clearance test and the plasma blood flow by diodrast. With ether anesthesia they found the same glomerular filtration and kidney blood flow as they did in the control studies, whereas with cyclopropane anesthesia there was a diminution in the inulin clearance and an increase in the blood flow in two subjects and a decrease in the blood flow in two others. They feel that these anesthetic agents have no harmful effects on the kidney.

Later in 1949, Burnett and his associates (50) made a more extensive study on patients, eight of whom had ether and seven

and does not alter the rate of repair of liver damage due to chloroform or eclampsia. The high oxygen concentration in the anesthetic mixture is held responsible in part for the lack of liver damage with cyclopropane anesthesia.

Orth and Stutzman (244), studying the effect of anesthesia upon kidney function as determined by the urea clearance test, found no reduction in the capacity of the kidney to eliminate urea after long periods of anesthesia in the dog. They state:

> The results of these tests seem to indicate that none of the three anesthetic agents studied—cyclopropane, ether and chloroform, interferes with kidney function as determined by urea clearance Since urea is the chief product of excretion in the urine and involves activity of both the glomeruli and tubules in filtration and reabsorption it is felt that such determinations give satisfactory indices of the effect of these anesthetic agents on the kidney.

Further evidence that cyclopropane anesthesia does not damage the kidney is that there is no increase in the non-protein nitrogen after anesthesia in man (229).

Waters and Schmidt state that the kidney function is depressed or an actual suppression occurs during anesthesia with cyclopropane, with a compensatory increase in secretion several hours following anesthesia. Mechling and Moffitt (209) found less evidence of nephritis following cyclopropane anesthesia than after anesthesia produced by nitrous oxide or ether in patients having comparable operative procedures.

There have been several papers on the effect of cyclopropane and ether anesthesia on kidney function in the experimental animal and in man during the past twelve to fifteen years.

In 1945, Craig and his associates (75), using dogs in eight experiments, obtained some very satisfactory information on the effect of these agents on the various functions of the kidney. They did not make urinary studies on the awakened animal but used a light plane of stage III for their control values and determined the urine output, creatinine clearance, and para-aminohippurate clearance or renal blood flow. They later put the dogs in deep surgical anesthesia, stage III, plane 3 to 4, and determined the

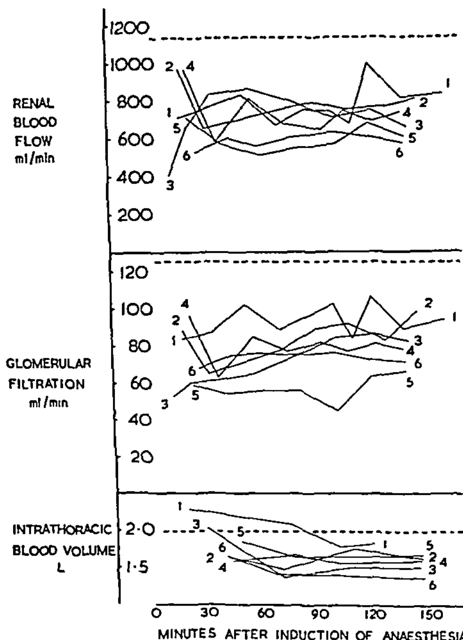


FIG 62 The effect of prolonged light cyclopropane anesthesia on the renal blood flow, glomerular filtration rate, and intrathoracic blood volume. The dotted lines represent an estimated mean value for normal conscious subjects (Lee *et al* Clin Sc., **12**, 169, 1953)

had cyclopropane anesthesia. They used mannitol for the glomerular filtration studies and para-aminohippurate for the renal plasma flow. They determined the renal function for ten to thirty minutes before anesthesia was started and then for thirty to seventy-five minutes after anesthesia had begun but before any surgical procedures had been carried out. Their subjects were maintained in stage III, plane 1 to 2, surgical anesthesia. They observed a decrease in urine flow of approximately fifty per cent with both ether and cyclopropane, a decrease of twenty-one per cent in glomerular filtration with ether, and thirty-one per cent with cyclopropane. The plasma flow as indicated by the para-aminohippurate clearance was decreased thirty-nine per cent with ether and fifty-two per cent with cyclopropane. They feel that ether is a better anesthetic as far as the kidney is concerned in patients in shock. This feeling is derived from the fact that there is less reduction in the blood flow to the kidney during ether anesthesia than during cyclopropane anesthesia.

Habif and his associates (138A) in 1951 followed the changes in renal blood flow, *glomerular filtration rate and urinary* output of electrolytes during cyclopropane anesthesia, operation and the immediate postoperative period in eleven patients, and found that the para-amino-hippurate clearance was reduced more than one-half and the inulin clearance was reduced one-half during the first part of the anesthesia period. The reduction in kidney function was due to an intra-renal vasoconstriction and became less as the duration of the anesthesia increased. They observed a rapid return of normal kidney function during the immediate post anesthetic period.

Lee *et al.* (180) in 1953 determined the effect of cyclopropane anesthesia upon glomerular filtration and renal blood flow in man using inulin and para-aminohippurate and found a decrease of glomerular filtrate of 50 per cent and of renal blood flow of 40 per cent early in anesthesia with a gradual return toward anesthetic values as anesthesia progressed. Their results are shown in *figure* 62.

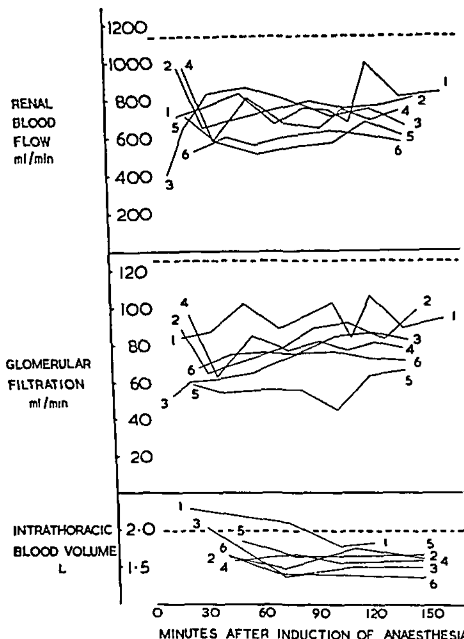


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8

The Clinical Administration of Cyclopropnae

For satisfactory clinical administration of cyclopropane, rebreathing in a closed system is essential. The explosive hazards and the cost of the gas per unit volume are so great that the escape of cyclopropane into the operating room cannot be tolerated.

The use of a closed anesthetic system is dependent upon the removal of carbon dioxide from the expired air and addition of oxygen to the mixture to replace that which is used. Jackson (156), 1916, was the first to use such a procedure experimentally for anesthesia in animals. He showed that after the animal was in the desired plane of anesthesia, it could be maintained in this level by rebreathing into a closed system in which the carbon dioxide was removed and oxygen added. The animal does not destroy the anesthetic, and the only need for adding extra ether after the desired plane was reached, was to replace that which was taken up by the fat and tissues of the body. Waters (338) was the first to adapt the observation of Jackson to clinical anesthesia. In discussing the contribution of Jackson to clinical anesthesia Waters states·

> In 1916 Dennis Jackson of the University of Cincinnati demonstrated that by absorbing expired carbon dioxide in alkali, animals could be confined indefinitely in a closed space containing an anesthetic mixture The only necessary addition to the mixture was, he found, sufficient oxygen from minute to minute to replace that used out of the mixture as it diffused into the blood from the animal's alveoli. He determined that there was no oxidation of the common anesthetic agents while in the body and practically no excretion, other than through the lungs. Jackson thus called attention to a fact which, when applied to clinical anesthesia, was destined to eliminate many of the unphysiologic side actions previously considered necessary accompaniments of inhalation anes-

DeWardener *et al.* (85) in 1953 studied the effect of elective hemorrhage, 13 to 29 per cent of total blood volume, upon glomerular filtration and renal blood flow in the patient lightly anesthetized with cyclopropane and found no significant change in either the glomerular filtration or renal blood flow.

From these studies and those described earlier, it seems quite obvious that neither ether nor cyclopropane has marked deleterious effects upon the kidney.

There are no experimental studies reported upon the effect of cyclopropane upon the ureters or bladder. Sanders and Fink (292) believe that there is less functional disturbance of the bladder after cyclopropane than after other agents, as the need for catheterization was reduced in patients after cyclopropane; Waters, on the other hand, found a slight increase in retention following cyclopropane anesthesia but attributed this to the type of cases and not to the anesthetic. Mechling and Moffitt (209) found more retention following cyclopropane than after ethylene or ether but less than after spinal.

SUMMARY

Cyclopropane anesthesia produces no liver damage detectable by the bromsulphthalein test.

There is a reduction of blood flow and glomerular filtration of about 40 per cent during cyclopropane anesthesia.

8

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The use of a closed anesthetic system is dependent upon the removal of carbon dioxide from the expired air and addition of oxygen to the mixture to replace that which is used. Jackson (156), 1916, was the first to use such a procedure experimentally for anesthesia in animals. He showed that after the animal was in the desired plane of anesthesia, it could be maintained in this level by rebreathing into a closed system in which the carbon dioxide was removed and oxygen added. The animal does not destroy the anesthetic, and the only need for adding extra ether after the desired plane was reached, was to replace that which was taken up by the fat and tissues of the body. Waters (338) was the first to adapt the observation of Jackson to clinical anesthesia. In discussing the contribution of Jackson to clinical anesthesia Waters states:

> In 1916 Dennis Jackson of the University of Cincinnati demonstrated that by absorbing expired carbon dioxide in alkali, animals could be confined indefinitely in a closed space containing an anesthetic mixture. The only necessary addition to the mixture was, he found, sufficient oxygen from minute to minute to replace that used out of the mixture as it diffused into the blood from the animal's alveoli He determined that there was no oxidation of the common anesthetic agents while in the body and practically no excretion, other than through the lungs Jackson thus called attention to a fact which, when applied to clinical anesthesia, was destined to eliminate many of the unphysiologic side actions previously considered necessary accompaniments of inhalation anes-

thesia. With a completely closed respiratory system and the absorption of carbon dioxide, the vapor of agents such as ether could be inhaled in a warm and moist atmosphere. The body temperature of patients subjected to long periods of anesthesia need no longer be expected to become depressed. Irritation and stimulation of the respiratory tract was less, resulting in quiet breathing during operation Reflex stimulation of perspiration from cold inhalations was less frequently seen, which, taken together with the maintenance of a completely moist atmosphere for inhalation, resulted in considerable reduction in visible water loss during the following operations. Quieter respiratory activity resulted in a decreased amount of work being performed during anesthesia. With the resultant decreased demand for oxygen, a greater margin of safety was made available in anesthesia with certain gases. The technical difficulties of administration were, in the main, simplified The quantity of anesthetic agents used was greatly reduced. The anesthetist no longer need choose one anesthetic agent for private patients and another for ward cases on the ground of a difference in cost. The atmosphere of operating rooms was no longer saturated with anesthetic gases and vapors. Fire and explosion hazards were thus greatly reduced and surgical teams found themselves free of the chronic effects of ether and other drugs.

MACHINES AND ACCESSORY APPARATUS FOR THE CLOSED TECHNIC

The anesthetic machines used at the present time are based on the work of Jackson. Two general types of carbon dioxide absorbers may be mentioned first, the to-and-fro absorbers, which were developed by Waters, are canisters of such capacities that one-half to one pound of soda lime will fill them. This canister is connected to the face mask by a slip joint; the other end of the canister is connected to the bag containing the anesthetic-oxygen mixture, thus the tidal air passes through the soda lime canister both during inspiration and expiration. Second, the circle absorber or filter as developed by Foregger (103) and Sword (323). In this type of absorber there are two large tubes connecting the face mask, filter, and anesthetic-oxygen reservoir, one an inspiratory and the other an expiratory tube; the circulation of the mixture through the soda lime is controlled by valves of different types. In either type one may shunt the mixture around the soda lime filter so that if it is desired, the carbon dioxide may be retained for a few minutes to stimulate respiration. See Woodbridge (347) for a detailed discussion of this subject.

The modern machine is built so that several gases are available for use when needed; all have flow meters of one type or another so that the anesthetist may know exactly how much of each agent is being added at any time. For the administration of cyclopropane the machine should have a fine flow meter if continuous administration is to be used throughout the anesthetic period, as advised by Burford (46) and Morris (223).

A closely fitting face mask is necessary for the use of the closed system during induction of anesthesia and is generally used throughout the anesthetic period; however, if it is indicated, a tracheal catheter, Magill or Guedel, may be inserted and attached directly to the anesthetic system.

PREMEDICATION

There are certain definite results which one expects to obtain by preanesthetic medication. Atropine or scopolamine is given routinely regardless of the other agents. Leake (179) in discussing "Chemical Adjuncts to General Anesthesia" states that "atropine was introduced as an adjunct to chloroform anesthesia in order to prevent reflex stoppage of the heart during the induction of chloroform anesthesia by paralyzing the peripheral endings of the vagi" and that its use should be reserved for this purpose; in relation to the use of scopolamine he states that

> in the absence of any critical evaluation of its usefulness as a preanesthetic hypnotic, there seems little justification for its continued employment merely because of a clinical routine or habit. It is chemically related to atropine and has somewhat the same type of action as atropine on the autonomic nervous system. This has no special value in preanesthetic medication, but may introduce deleterious factors

With the amount of these drugs given (.3 to .65 mgm.), the reduction of secretion from the glands of the oral and respiratory mucosa is the main beneficial effect; neither atropine nor scopolamine in these amounts produces any peripheral paralysis of the vagus to the heart, but both may stimulate the vagus center and cause a slowing of the pulse. McGuigan (204), Harris (142),

Platz (256), and Kochman (172) have shown that atropine or scopolamine in doses of .75 mgm. or less subcutaneously actually reduces the heart rate 12 to 15 beats per minute; however, if the dose of atropine is increased to 1.2 to 2 mgm., there is a marked rise in rate after 15 to 30 minutes, but this rise is usually preceded by a definite reduction in rate as shown by Sturgis *et al.* (315). Smith *et al.* (306), Crawford (76), and Nicholson (230) have shown that doses of atropine of 1 mgm. or more will release the effect of the vagus upon the heart rate, but this dose is larger than the one used clinically in anesthesia.

The other agents—morphine, opium, barbiturates, avertin, and so forth—are given with several aims in mind: first, to put the patient in a quiet state and relieve anxiety; second, to make induction of anesthesia easier for the patient; third, the amount of premedication given is often of such magnitude that it is expected to reduce markedly the concentration of the inhalation anesthetic necessary to produce the desired level of anesthesia.

Practically all anesthetists believe that the amount of the preanesthetic medication should be reduced when cyclopropane-oxygen is to be given because of the lack of respiratory stimulation produced by cyclopropane. Waters and Schmidt advise the use of morphine, 8 to 16 mgm., with scopolamine, .32 to .65 mgm., given subcutaneously one and one-half hours before cyclopropane; others who advise similar premedication are Stiles, Neff, Rovenstine, and Waters (313), Rovenstine (286), Burford (48), Moffitt and Mechling (217), and Sanders (291). Neff and Stiles (229) used similar premedication in diabetic patients.

Several, particularly Griffith (123), Bogan (30), and Wood (346), prefer to use avertin, 70 to 80 mgm. per kilogram, as a basal anesthetic in place of morphine.

Pentobarbital (Nembutal) has been used either alone or with morphine. Griffith (123), Morgan *et al.* (219), and Eversole (96) give 100 to 200 mgm. per average adult, which is a rather large dose.

In relation to the use of morphine as preanesthetic medication,

it would be of interest to know if barbiturates would abolish the cardiac irregularities in man as they do in dogs under morphine-cyclopropane anesthesia, as shown by Robbins, Baxter, and Fitzhugh (279). A carefully controlled electrocardiographic study on clinical patients would probably show that the barbiturates would give protection as is indicated in the last sentence of an excerpt from The Lancet of September 23, 1939, page 704 (10):

> The increasing use of cyclopropane gives importance to the selection of the most appropriate drug for premedication when one wants to give some adjuvant sedative or hypnotic before the anesthetic itself. The fact that cyclopropane is in no sense a respiratory stimulant—wherein it differs from some other anesthetics—would in itself probably make anesthetists chary of using beforehand any agent that tends to depress the breathing. Chief among these is morphine, and the belief that this should be avoided before administering cyclopropane is strongly supported by some experimental studies in the United States.* These show that dogs given morphine before cyclopropane react less favourably to the anesthetic. Not only is respiratory arrest more readily brought about but also certain irregularities appear before the respiratory arrest—a phenomenon rarely met in dogs having cyclopropane alone On the other hand, the investigators found that barbiturates given beforehand had a beneficial effect, to the extent that dogs treated with them behaved better not only than those which had morphine but also better than those given cyclopropane only. They believe that whereas cyclopropane intensifies the bradycardia and arrhythmia of dogs given morphine, the barbiturates lessen vagal tone and decrease the irritability of the automatic tissues of the heart; a barbiturate should therefore be given in place of morphine when cyclopropane is used clinically These experiments will confirm a practice that has already been adopted, on experimental grounds, by a good many of the anesthetists who have wide experience of cyclopropane.

The paragraph immediately above the quotation from The Lancet, was written at a time in which we were pharmacologists with no experience in the clinical use of anesthetics. Since that time, our position has changed and we have become anesthesiologists with an interest in the pharmacology of the anesthetic agents and their effect upon the human subject. We have, during the past few months, been running a study upon the electrocardio-

* Robbins, B H., Baxter, J H., Jr , and Fitzhugh, O G Ann. Surg., **110**, 84, 1939 (279)

graphic changes during intubation under cyclopropane anesthesia and during the anesthesia for the operative procedure and have been interested in the preanesthetic medication in relation to any changes that may occur and also the effect of intravenous drugs, barbiturates, or atropine upon termination of cardiac arrhythmias that develop during the operative procedure. Our procedure was to take a control record using lead II before the anesthesia was started. The subject was then anesthetized with a cyclopropane and oxygen mixture of approximately twenty-five per cent cyclopropane. When the plane 2 of surgical anesthesia was reached, the viso-cardiette was started running and the intubation made with continual recording of the electrocardiogram until the subject was intubated and reconnected to the gas machine by way of the inspiratory and expiratory tubes. At intervals of fifteen minutes or less thereafter throughout the procedure, records were made, and in addition, upon any evidence of arrhythmias either by looking at the movement of the stylus or that might be suspected by palpation of the pulse, further electrocardiograms were made and analyzed for any possible arrhythmias.

The first group of patients, 64 in number, received only phenobarbital, approximately 1 mgm. per pound, and atropine for preanesthetic medication. Three of the 64 patients showed arrhythmia before anesthesia. During the induction period arrhythmias were observed in 9 patients, 5 with bigeminal rhythm, 3 with auriculoventricular nodal rhythm and one with premature ventricular systole, which persisted during intubation, and one patient developed multiple focus ventricular extra systoles immediately following intubation. As a rule, 10 to 15 seconds elapsed from the time the viso-cardiette was started until laryngoscopy and intubation were completed and about 20 to 25 seconds until the anesthetic system was reconnected and respiration supplemented by pressure in the breathing bag. Cardiac arrhythmias were noted during induction and/or during anesthesia for the operative procedure in a total of 16, or 25 per cent, of the 64 patients who received barbiturate premedication, these were 3 with auriculo-

ventricular nodal rhythm, 3 with premature ventricular systole, one with multiple focus ventricular systole, and 9 with bigeminal rhythm.

The intravenous injection of secobarbital, 1 mgm. per kilo, was effective in correcting the arrhythmia, within 20 to 40 seconds, in six of seven patients with bigeminal rhythm and in one of three patients with auriculoventricular nodal rhythm. Records from two patients in this series all shown in figures 63 and 64.

The second group of patients, 50 in number, received only morphine, 1 mgm. per 15 pounds body weight, and atropine for preanesthetic medication. During the period of induction of anesthesia and before intubation arrhythmias were noted in 11 patients, 2 with bigeminal rhythm, 3 with auriculoventricular nodal rhythm and 6 with multiple focus ventricular extrasystole, and

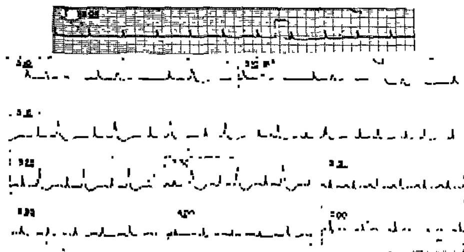


FIG 63. Electrocardiographic records from patient F , female, age 50, weight 120 pounds Operation transthoracic repair of traumatic perforation of the esophagus. Soluble phenobarbital .12 gram at 1:30 P.M , atropine 0004 gram at 2:30 P M Control record at 3.04 P M. Cyclopropane-oxygen at 3:05 P M Endotracheal intubation between 3 10 and 3:10 15" The bigeminy, which was present before intubation persisted even with excessive supplementation of the respiration until 3.30 P.M at which time seconal, 75 mgm , was given intravenously. The rhythm reverted to normal within 30 seconds and remained so throughout the operation

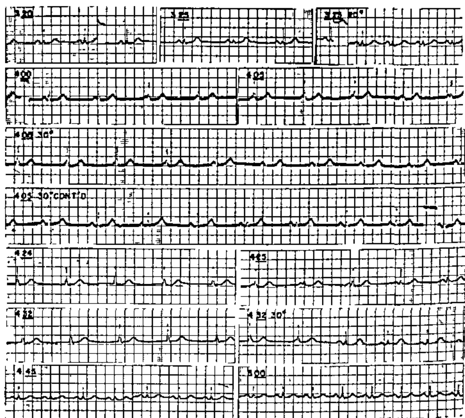


FIG 64 Electrocardiographic records from patient A , female, age 60, weight 120 pounds Operation for intestinal obstruction. Soluble phenobarbital .12 gram at 1:30 P M , atropine 0004 gram at 2:30 P M. Control record at 3:20 P M , cyclopropane-oxygen at 3:21 P M. Endotracheal intubation between 3:25 and 3:25 30" P.M At 4:00 P M A-V dissociation recorded and at 4:05 seconal 50 mgm. given by antecubital vein, with reversion to normal in 30 seconds for a period of 18 minutes when nodal rhythm was noted At 4:24 a second injection of seconal 50 mgm. was given, and normal pace maker re-established for 5 minutes. At 4:32 atropine sulfate .1 mgm was given by vein, and the sino-auricular node became dominant and remained so through the remainder of the anesthesia.

bigeminal rhythm was noted in two more patients immediately following intubation. Cardiac arrhythmias were noted during induction and/or during anesthesia for the operative procedure in a total of 29, or 58 per cent, of the 50 patients who received morphine as preanesthetic medication: there were 8 patients with auriculo-

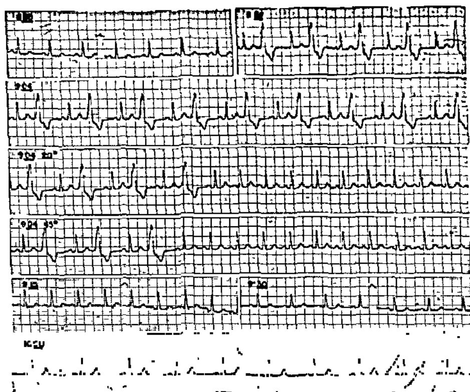


FIG. 65 Electrocardiographic records from patient L, female, age 45, weight 150 pounds. Operation, cholecystectomy. Morphine sulfate 01 gram at 6:30 A M., atropine .0004 gram at 7:30 A M Control record at 8:50 A.M. Cyclopropane-oxygen anesthesia at 8:53 A M Endotracheal intubation immediately following record at 8:57 A M. The bigeminy with single focus ventricular extrasystole persisted until 9:04, at which time seconal 75 mgm was given by vein and the rhythm became regular at 9:04 45" and remained so during the anesthesia

ventricular systole, 10 with bigeminal rhythm and 8 with multiple focus ventricular systole.

In 21 patients in whom the arrhythmia persisted sufficiently long to warrant the use of secobarbital, 1 mgm. per kilo, intraven, ously the rhythm was returned to normal, within 20 to 40 seconds after the injection, in 16 of 17 patients that had premature ventricular systole, bigeminal rhythm or multiple focus ventricular systole, but was of no value in 4 patients that had auriculoventric-



FIG. 66. Electrocardiographic records from patient B , female, age 53, weight 140 pounds. Operation cholecystectomy and repair of ventral hernia. Morphine sulfate 01 gram at 6:00 A M., atropine 0004 gram at 6:45 A M. Control record at 8:00 A.M. Cyclopropane anesthesia at 8:01 A M. Endotracheal intubation between 8:05 and 8:05 30" A.M Marked ventricular arrhythmia between 8:08 and 8:13 A M , at which time seconal 70 mgm. was given by vein. Rhythm became regular in 24 seconds and remained so throughout the operation.

In no instance in the cases above (figs 63–66) was the concentration of cyclopropane in the anesthetic system reduced by the rapid addition of oxygen

ular dissociation or nodal rhythm. Records from two patients from this series are shown in figures 65 and 66.

Thus in 22 of 24 patients in the two series in which the arrhythmia was of ventricular origin the intravenous administration of secobarbital was effective in causing a return to normal rhythm whereas in only one of 7 cases where the arrhythmia was of supraventricular origin was the rhythm reverted to normal and in this one instance the duration of effect was for only 15 to 20 minutes; atropine, 0.2 mgm., intravenously caused a permanent return to normal in this patient. See figure 64.

When one compares the data in our patients receiving barbiturate premedication where the frequency of cardiac arrhythmias was 25 per cent with those of our patients receiving morphine premedication where the frequency of arrhythmias was 58 per cent, and with the data of Burstein et al (53) where the frequency of arrhythmias during intubation in patients premedicated with morphine and given cyclopropane was 62 per cent and combined with the observation in 22 of 23 patients showing the most fre-

quent types of arrhythmias observed during cyclopropane anesthesia that the intravenous administration of secobarbital was followed with a reversion to normal rhythm, one comes to the conclusion that barbiturates are to be preferred over morphine for premedication of the patient that is to receive cyclopropane.

Joseph and Denson (83A) in 1954 reported a careful study upon cardiac rhythm and endotracheal intubation under cyclopropane anesthesia. Their procedure was to have a continuous recording of the electrocardiogram from the control period before the beginning of the anesthetic through the induction, the intubation and the immediate post-intubation period. Their patients were given meperidine and atropine or scopolamine premedication and induced with cyclopropane and oxygen or with 50 to 200 mgm. thiopental. Anesthesia was then deepened with cyclopropane until the patients were sufficiently relaxed for endotracheal intubation to be completed with ease. This depth of anesthesia required controlled respiration and all patients were apneic during the maneuvers of intubation. In only 4 instances in two cases were arrhythmias produced during the period of intubation and these were due to inadequate ventilation and excess digitalization. In 19 of 106 cases arrhythmias were observed within 6 seconds to 4 minutes after intubation and 1 second to 3 minutes after controlled respiration with oxygen had been resumed. These arrhythmias were corrected within 30 seconds to 9 minutes by increasing or improving the pulmonary ventilation presumably with oxygen alone.

REACTION OF THE ORGANISM OR SIGNS OF ANESTHESIA

The reactions of the organism or signs of anesthesia with cyclopropane are fairly close to those with ether, the most marked difference being that of lack of respiratory stimulation with cyclopropane, this is due probably to the lack of irritation to the respiratory tract and the high oxygen content of the cyclopropane-oxygen anesthetic mixture.

The first stage, or analgesia, is produced in the non-premedicated man with a 6 per cent concentration (298). Due to the

potency of cyclopropane and its rapid absorption, stage II, or the stage of excitement and delirium, is usually not observed. Stage III, plane 1, is reached when breathing becomes regular and the eyeballs oscillate; in the premedicated subject about 7 per cent cyclopropane is required for this plane of stage III. As the patient passes through the first plane, there is a reduction of eyeball *movement, and when plane 2 is reached, the eyeball* is still and the pupil centrally located in the palpebral slit; 13 per cent cyclopropane is necessary for this level. During the third and fourth planes of stage III there is a gradual reduction of the amplitude of respiration; 23 per cent cyclopropane is sufficient to bring the subject to this level. Respiratory arrest, or stage IV, is reached with an average of 42 per cent cyclopropane (Waters and Schmidt (341)).

In the deeper planes of stage III, very careful and almost continuous observations on the pulse rate and rhythm and amplitude of respiration are necessary. Due to the high oxygen content, the color of the patient remains pink even after intercostal paralysis, but if the concentration of cyclopropane is too high, changes in the rate or rhythm of the pulse will develop, and then the cyclopropane should be reduced by the rapid addition of oxygen.

Eversole, Sise, and Woodbridge (96) believe that the signs of anesthesia as outlined by Guedel (200) are satisfactory for cyclopropane if induction is not too rapid and if changes in the levels of the third stage are brought about gradually. They advise close observation of the pulse and pressure.

Guedel, in his discussion of cyclopropane anesthesia, states that *the classification of the signs of anesthesia that he described* in 1923 is not applicable to the patient under cyclopropane anesthesia. He depends upon the following for his determination of the planes of anesthesia· First, the respiration; second, the color of the patient; and third, muscular relaxation. A supplement to these is the A.C.R., arteriolar capillary refill time, which he first described and stated as a satisfactory rough estimation of the circulatory function of the patient. This is the time necessary for

the refilling of the capillaries after they have been blanched by pressure.

Romberger (283) has given a concise description of the signs of anesthesia under cyclopropane. He is of the opinion that the action of cyclopropane is so rapid that there is no need to differentiate between stage I (analgesia) and stage II (delirium), or to separate stage III (anesthesia) into the customary four planes so carefully described by Guedel (132). Romberger divides the procedure into three levels: first, *induction*, from the awakened state to the loss of the lid reflex; second, *moderate anesthesia*, that level of surgical anesthesia during which the eyeball oscillates; and third, *deep anesthesia*, in which the eye is centrally fixed and there is a reduction of respiratory activity. As the stage of respiratory arrest is approached, both the depth and rate of respiration are reduced.

Eversole, Sise, and Woodbridge (96) state that if induction is rapid, the established signposts of the depths of anesthesia are not as well marked as with ether; however, they feel that if induction is fairly slow, the different levels may be satisfactorily ascertained. The first and second stages are rapidly passed without, as a rule, any delirium or excitement. The third stage, or first plane of surgical anesthesia, is entered at the time of abolition of the lid or wink reflex. The second plane is entered as the movements of the eyeball cease. As one progresses in the second plane to the third, the pupils begin to dilate, and further increase in depth leads to a reduction of rate and amplitude of respiration. They feel that close observation upon the respiratory activity is of greatest value in determining the condition of the patient.

Waters and Schmidt (341) attribute the difference of physical signs under cyclopropane from those under ether to two characteristics of cyclopropane: first, it has very little irritant effect upon the respiratory tract, so that the patient will inhale high concentrations without the production of laryngospasm, which is a protective mechanism against the inhalation of too high concentrations of other agents, second, cyclopropane is not a respira-

tory stimulant, and because of the high oxygen content of the anesthetic mixture, respiration is not increased unless carbon dioxide is permitted to build up to a high concentration. They *find that the abolition of the lid reflex is indicative of entrance* into stage III (surgical anesthesia) and that cessation of oscillation of the eyeball occurs as one enters plane 2 of stage III. Planes 3 and 4 cannot be separated because there is a gradual diminution of amplitude of respiration as the intercostal activity is abolished and diaphragmatic breathing takes over the load of respiratory effort. The fourth stage is reached as respiratory activity stops.

TECHNIC OF THE ADMINISTRATION OF CYCLOPROPANE

After the premedication has been given and sufficient time has elapsed for the desired effect to be fully developed, usually thirty to ninety minutes depending upon the type and route of administration of the preanesthetic drug, the cyclopropane may be started.

There are many modifications of technic for administering cyclopropane for anesthesia, but certain generalizations are possible. Usually the bag is filled with oxygen so that it will be more than adequate for tidal exchange (1000 to 3000 cc.). The mask is then placed on securely; oxygen at 500 cc. per minute and cyclopropane at 200 to 500 cc. per minute are run in until the patient enters the third stage, at which time the flow of oxygen is reduced to the metabolic need (about 200 to 300 cc. per minute) and cyclopropane is cut to about 100 cc. per minute. This flow is continued until the desired plane is reached, at which time the flow of cyclopropane may be continued at 20 to 50 cc. per minute or stopped entirely for several minutes. The continuous administration of a very small amount of cyclopropane should give a *more constant level of anesthesia than the intermittent addition* of cyclopropane. During the maintenance of anesthesia it is necessary to add only enough cyclopropane to balance that which escapes into the operating room and to replace that which is deposited in the fat and tissues of the body.

The carbon dioxide filter may be cut out of line during the induction, or it may be left in; induction is more rapid with it out, but some feel that it is better for safety to leave it in all the time.

If the anesthesia becomes too deep, the dilution of cyclopropane by a rapid flow of oxygen into the bag will soon bring the patient back to a lighter level.

Eversole, Sise, and Woodbridge (96) use the following technic. The induction is started with the soda lime filter excluded from the breathing circuit, and it is switched into the circuit later as respiratory stimulation, due to accumulation of carbon dioxide, is noted. After the bag is sufficiently filled to be adequate for tidal exchange, the mask is placed on and oxygen at 1000 cc. per minute and cyclopropane at 200 cc. per minute are started. The flow of cyclopropane is then increased by 100 cc. units until 500 cc. per minute flow is reached; at least two breaths are taken between each increase of flow. The oxygen flow is cut to 500 cc. per minute and the flow of cyclopropane at 500 cc. maintained until surgical anesthesia is produced, after which cyclopropane is cut to 50 to 100 cc. per minute until the patient is more or less equilibrated with the cyclopropane concentration in the bag. Then the flow of cyclopropane may be stopped completely, but they feel that a given level can be best maintained if there is a continuous flow at a low rate.

Sahler and his associates (290) have reported on the use of cyclopropane in 7,120 cases and have some very pertinent comments to make in relation to its advantages and disadvantages. Among its advantages are (1) the induction period is comparatively fast and pleasant, (2) it may be given with the high concentration of oxygen, (3) the depth of respiratory excursion may be controlled, thus making the gas an ideal anesthetic for lung surgery, and (4) under full anesthesia there is quiet breathing and complete relaxation. The undesirable features are (1) it is explosive in anesthetic concentrations, (2) there is somewhat more bleeding under the anesthetic than most others, (3) there is danger of respiratory paralysis when complete relaxation is obtained, and

(4) the patient passes from one plane to another plane of anesthesia faster than with almost any other agent. They feel that premedication should be fairly large in that induction was easier in the patient that was quiet. Morphine and scopolamine or soluble pentobarbital and seconal were used as the preanesthetic drugs. For induction of anesthesia, their technic was as follows: the bag was filled half full with oxygen and the mask applied to the patient's face. After a few breaths, cyclopropane was admitted at the rate of 600 to 700 cc. per minute while oxygen was flowing at 250 to 500 cc. After anesthesia was induced, the flow of cyclopropane was cut to 40 to 150 cc. per minute and that of oxygen maintained at 250 to 500 cc. These flow rates give rise to a concentration that would produce anesthesia in a relatively short period of time and produce it quite safely. They feel that when an operative procedure has been of quite some length, carbon dioxide inhalation intermittently for the twenty-four to forty-eight hours immediately following the anesthesia is of benefit in maintaining the patient in a satisfactory state.

A most satisfactory technic for the rapid induction of anesthesia in the average adult is by the following method. The bag, of approximately five liters, is filled with a mixture containing equal amounts of oxygen and cyclopropane. If one assumes that the residual air in the chest of the patient and the volume of the tubes and the dead space in the setup totaled approximately five liters, then when the mixture of cyclopropane and oxygen in the bag is mixed with that of the dead space in the patient's lungs and the tubes, one would end with a mixture containing approximately twenty-five per cent cyclopropane, thirty-five per cent oxygen, and forty per cent nitrogen. After three or four breaths on this mixture of fifty per cent oxygen and fifty per cent cyclopropane, the flows are reduced to 300 cc. of oxygen and 100 cc. of cyclopropane per minute; in two to three minutes on this mixture the patient will be in plane 1 to 2 of surgical anesthesia. If deeper levels are needed, it could be maintained at that flow, but if that level is sufficient, then the flow of cyclopropane could be cut down

to 25 to 50 cc. per minute with the oxygen at the rate of approximately 300 cc. per minute or the average rate of oxygen consumption in the individual.

France (104) has published a description on cyclopropane anesthesia, a technic suitable for infants, in which he states that he used only atropine for preanesthetic medication without any other drugs which might depress respiration. He uses a relatively high flow rate of 1.25 liters per minute of oxygen, 3 liters per minute of nitrous oxide, and 750 cc. per minute of cyclopropane which give a concentration of approximately 15 per cent. France particularly liked the high flow in that after long operative procedures, there was no so-called cyclopropane shock observed. Smith (304), in his comments on this paper, has this to say:

> Two recommendations are made in this paper. The first, that cyclopropane be used for infants is unquestionably an excellent one. Cyclopropane is extremely well suited for use in infants and it only seems unfortunate that it has not been more widely accepted.
>
> The second recommendation is that cyclopropane be administered in semi-closed technique flowing at 750 cc. per minute with oxygen and nitrous oxide at 1 25 and 3 liters respectively. This specific technique is chosen because of the theoretic objections to methods using lower flows of gases, namely, that soda lime offers resistance to respiration, that bleeding is increased and that there is increased risk of cyclopropane shock.
>
> The high flow rate of cyclopropane suggested in this paper seems expensive and relatively dangerous from the explosive standpoint. The objections to low flow technique are perhaps over emphasized Administration of cyclopropane by a to and fro method has been the standard procedure for poor risk and premature infants for some years at Children's Hospital in Boston. Flow rates have been in the range of 150 to 200 cc of cyclopropane and 400 to 500 cc. of oxygen per minute This flow allows for occasional rinsing of the system to wash out carbon dioxide
>
> McQuiston of Chicago has had excellent results with a truly closed to and fro system in infants using flow rates of 5 to 10 cc. of cyclopropane and 100 to 125 cc of oxygen Naturally, respiration must be assisted in any technique using cyclopropane

Due to the rapid rate of absorption and elimination of cyclopropane one may very readily increase or decrease the depth of

anesthesia by the addition of more cyclopropane or oxygen, respectively.

During the anesthetic period the rate and rhythm of the pulse and rate and amplitude of respiration should be watched carefully. Any quick change from a normal pulse rate and rhythm to a marked bradycardia, tachycardia, or arrhythmia demands a reduction of the concentration of cyclopropane in the bag by the addition of oxygen; likewise, the development of a slow, shallow respiration indicates that the patient is too deep even though there is no sign of cyanosis, and oxygen should be added to reduce the concentration of cyclopropane in the bag.

The recovery from cyclopropane anesthesia is rapid when compared to ether. Due to the fact that at the end of anesthesia with cyclopropane-oxygen there is little or no slowly absorbable gas in the lungs, it is desirable to have the patient rebreathe a mixture of air and oxygen or helium and oxygen before the mask is removed; in fact, Burford (47) advises the use of a small amount of helium throughout the anesthetic period to prevent atelectasis due to collapse of the alveoli because of complete absorption of the cyclopropane-oxygen mixture.

In his paper of 1945, Waters (340) has summarized his impressions gained over a period of fifteen years in the use of cyclopropane in about 25,000 patients at the Wisconsin General Hospital. Of major importance in preparing the patient for the operative procedure is that of premedication, and with cyclopropane Waters feels that somewhere between one-quarter and one-half of the ordinary dose of morphine and barbiturate suffices for the premedication, without producing a marked depression of respiration. He feels that the respiratory depressant action of the preanesthetic drugs plus the depressant action of cyclopropane on respiration when combined in ordinary doses depressed the respiration too much and recommends that the preanesthetic medication be cut to one-fourth or one-half of the ordinary dose. He feels that either scopolamine or atropine may be used to depress the parasympathetic division of the autonomic nervous system

in relation to salivation and bronchial secretion. In his earlier work, both in the laboratory and in the clinic, the effect of cyclopropane on the cardiovascular mechanism was very carefully observed, and the bradycardia of sixty to seventy per minute was almost routine in patients that were skillfully and deeply anesthetized. Occasionally the pulse would drop to as low as 50, and not infrequently under such conditions a tachycardia might soon ensue unless, as he states, the concentration of cyclopropane in the inspired mixture be rapidly reduced by the addition of oxygen to the mixture. He has found no need to add ether, barbiturate acid derivatives, or procaines to the patient in order to prevent bradycardia or arrhythmias because he feels that dilution of the cyclopropane with oxygen is a more satisfactory method of control. He does not feel that circulatory disease is a contraindication for the use of cyclopropane if a general anesthetic agent is needed. His last paragraph in the summary is an excellent and brief description of what can be done with cyclopropane from a beneficial effect and also what may be undesirable. "My experience of nearly fifteen years with cyclopropane leaves me with the personal impression that this agent permits rapidity of control of the depth of anesthesia impossible with other inhalation agents. However, this very fact may result in unfortunate and disastrous results when ignorance or carelessness accompany the administration."

In 1951, Griffith (125) reported on the results of his observation on some twenty thousand personally administered anesthesias with cyclopropane, and most of these observations were made during a period in which approximately ninety-six per cent of all the surgical procedures were carried out under cyclopropane anesthesia. Of particular interest in this summary are those ideas that he presents under the heading of "Keeping Out of Trouble", of which there are four primary principles: (1) Maintenance of a free and unobstructed airway. He does not require the intubation of every patient that is to get cyclopropane, but he will intubate on the slightest provocation. "I will not give a cyclopropane anesthesia anywhere, even for the most minor procedure, without

having immediately available a laryngoscope and endotracheal tube. This is the kind of insurance that pays off in an emergency." (2) The maintenance of adequate pulmonary ventilation for two reasons: First, to insure adequate oxygen to the tissues; second, to remove the carbon dioxide as it is formed in the body. (3) The maintenance of a smooth level of anesthesia. (4) Keeping the concentration of cyclopropane as low as possible as long as adequate anesthesia is present. He is in agreement with Dripps that the cyclopropane shock which one occasionally sees after a prolonged anesthesia with cyclopropane is due to an abnormal build up of carbon dioxide in the blood during the operative and anesthetic procedure, and as soon as this is terminated, the fall in pressure results from the rapid blowoff of the carbon dioxide. In his wide personal use of cyclopropane, he has not found it necessary to avoid the use cyclopropane in patients with organic heart disease. In fact, he prefers to use cyclopropane in patients with cardiovascular disease for several reasons: First, cyclopropane is nonirritating Second, it is used with adequate or excess oxygen so hypoxia is much less likely with cyclopropane in oxygen than with other agents. If, during the cyclopropane anesthesia, cardiac irregularities develop and persist, he prefers to reduce the concentration of the anesthetic and use a relaxing agent like curare to produce the relaxation in a lighter plane of surgical anesthesia. I should like to quote the final lines of his paper on the clinical evaluation. "The anesthetist who uses cyclopropane should not be afraid of it but he should know what he is doing. Eternal vigilance is the price of safety."

There are two papers in the literature which deserve singling out for their excellence and for the information one may gain by reading just these two, if nothing else. They are "Cyclopropane Anesthesia" by Waters and Schmidt in 1934 (341) and "The Present Status of Cyclopropane," report of Council on Pharmacy and Chemistry of the American Medical Association (71). The information contained in these two papers forms a satisfactory basis from which one may continue further reading on cyclopropane as an anesthetic agent.

9

Complications During and Following Cyclopropane Anesthesia

Postoperative complications following cyclopropane anesthesia are no more frequent nor of different types than those observed following the use of other inhalation anesthetics.

Gebauer and Coleman (107) reported a case of postanesthetic encephalopathy following cyclopropane anesthesia. The patient was under cyclopropane for two hours and thirty-five minutes for a thoracoplasty. Late in the operation there was a fall in pressure to 90/60 with a rise in pulse rate from 70 or 80 to 145; after completion of the operation and return to the ward, the pressure was 115/60 three hours later, but during this period there was cyanosis for some thirty minutes. The patient never became rational after the anesthesia and died seven days later. Autopsy with pathological examination of the brain showed changes similar to those produced by anoxia. An excerpt from the report of the neuropathologist is given below:

> There is a remarkable resemblance of these changes to those seen in the brain damaged by ischemia from vascular occlusion which leaves little doubt that the encephalopathy described (which is a pure degenerative process) is of anoxemic origin.

In discussing the possible factors in this case the authors believe that anoxia was the most probable cause of the disturbance.

Griffith (124) reported a case under cyclopropane anesthesia which developed convulsions forty minutes after the nose was packed with 2 per cent nupercaine for submucus resection of the nasal septum; the first signs were twitching in the hands and arms, with rapid extension to the muscles of the neck and face. Oxygen was given without results; coramine increased respiration but

made the convulsions worse. Amytal, .5 gram intravenously, stopped the convulsions immediately and the patient had no further trouble. *Griffith believes that the convulsions were related* to nupercaine intoxication and not to the cyclopropane.

Headache and excitement were about as frequent after cyclopropane as after ether or ethylene in the cases reported by Waters and Schmidt (341).

Tidmore (336) mentioned no central nervous system disturbances in his series of patients, some of which were under cyclopropane anesthesia for six to eight hours. Moffitt and Mechling (217) found more headache after cyclopropane anesthesia than after nitrous oxide but less than after ether, ethylene, or spinal anesthesia in patients having major operations.

There have been several reports on the postoperative respiratory complications following cyclopropane anesthesia, with comparative data using other anesthetic agents. Those reports of Waters and Schmidt (341), Taylor, Bennett, and Waters (326), Moffitt and Mechling (217), and Burford (48) show that cyclopropane anesthesia produces less respiratory complications than ether and other agents.

In the data of Taylor *et al.* (326), compiled from 12,349 cases, there are certain definite facts established, and these are that regardless of the anesthetic agent used, the incidence of postoperative respiratory complications increases with the increase of duration of the anesthesia, with increase in depth of anesthesia, and with increase in grade of the surgical risk. A summary table (table 51) of postoperative respiratory complications classified according to the anesthetic used and type of morbidity is given

These data show that the postoperative pulmonary complications *are no more frequent after cyclopropane anesthesia than* after other agents and that the major complications are less with cyclopropane than with ether.

Burford (48), in his study of postoperative pulmonary complications, found an incidence of .97 per cent in 1,333 cases anesthetized with cyclopropane. He reported that, in abdominal cases in which

TABLE 51*

Postoperative respiratory complications

	Total Cases				
	C_3H_6 5,889	Ether 2,431	N_2O 1,299	Ethylene 1,019	Procaine 1,209
	per cent	per cent	per cent	per cent	per cent
Major complications					
Pneumonia	0.63	0.91	0.46	0.29	1.57
Massive collapse	0.10	0 29	0	0.10	0.16
Partial collapse	0.20	0 62	0.38	0.59	0.16
Pulmonary edema	0.02	0	0	0	0
Total	0.95	1.82	0 84	0.98	1 89
Minor complications					
Cough	5.27	5.80	3 77	6.96	6.45
Pharyngitis or laryngitis	2.14	1.60	2.77	2.65	1.07
Bronchitis or tracheitis	0.27	0 68	0 15	0 29	0.32
Other minor complications	1.49	2 67	1 38	1.67	4.05
Total	9.18	10 65	8 08	11.58	11.92

* Taylor, Bennett, and Waters: Anesth. and Analg., 16, 189, 1937 (326).

cyclopropane was supplemented with ether, in 303 patients the incidence of respiratory complications was 2.97 per cent, whereas in 214 cases under cyclopropane alone the incidence was only .93 per cent.

Jones and Burford (162) reported four cases of massive atelectasis following cyclopropane anesthesia, three of which were confirmed at autopsy, the fourth patient showed signs of massive collapse three minutes after the anesthetic was discontinued, respiration stopped, and the patient became very cyanotic, after which the heart begain to fail, artificial respiration and the administration of oxygen produced a return to normal in a few minutes.

The massive atelectasis or pulmonary collapse following cyclopropane-oxygen anesthesia is thought to be due to the rapid absorption of all the cyclopropane and oxygen in the distal alveoli, which in the absence of a slowly absorbable gas (nitrogen) causes

the alveoli to collapse. Jones and Burford advise the addition of helium to the anesthetic mixture to prevent this collapse.

Moffitt and Mechling (217), comparing the frequency of postoperative pneumonia in 200 cases under each anesthetic, found the incidence after cyclopropane to be the same as after ether but less than that after nitrous oxide and spinal anesthesia.

Griffith reported a case of acute pulmonary edema in a patient anesthetized with cyclopropane for repair of a hernia. After the operation was about half through, cyanosis became noticeable and, on inserting an airway, sero-sanguinous fluid came from the trachea; a total of about 12 ounces of this fluid was aspirated through the tracheal catheter, after which the operation was completed and the patient recovered rapidly. No satisfactory explanation of the cause of this disturbance could be found.

The effects of cyclopropane anesthesia upon the heart rate and rhythm have been discussed in detail in Chapter 3.

Waters and Schmidt (341), Eversole *et al.* (96), and others have called attention to the bradycardia, arrhythmia, and rapid change of pulse rate during anesthesia with cyclopropane. There is a difference in the reports of various anesthetists upon blood pressure changes during anesthesia; Waters (339) and Sise *et al.* (301) found no constant change, whereas Rowbotham (288) and Bogan (29) found rises routinely of 10 to 40 mm.

Kurtz, Bennett, and Shapiro (175) found electrocardiographic changes in a very high per cent of all cases under ether, chloroform, cyclopropane, ethylene, nitrous oxide, and procaine anesthesia, but in only the patients under cyclopropane were multiple focus ventricular extrasystoles observed, and since this type of arrhythmia is frequently seen in experimental animals before fibrillation, it may be of serious nature in man.

There have been several cases reported of circulatory collapse and death with cyclopropane anesthesia. Waters (339) reported two that were probably due to ventricular fibrillation. Both were in deep planes of stage III anesthesia before the trachea was intubated; neither breathed spontaneously after intubation. Epi-

nephrine was injected directly into the heart in one patient, and from Meek's (210) later studies this might produce fibrillation.

Cohn (63) reports having had four cases with simultaneous respiratory and circulatory failure during cyclopropane anesthesia; in three of the cases failure developed very soon after cyclopropane was started. Three were given epinephrine intravenously, and two of these recovered.

Guedel and Knoefel (133) describe a case which probably died of ventricular fibrillation. This patient had been inhaling cyclopropane-oxygen for only twenty to thirty seconds when she screamed, took one deep breath and became rigid; immediate palpation over the carotid and auscultation for heart sounds gave no evidence of cardiac activity. In view of the similarity of these circulatory failure cases with those under chloroform, and the fact that Meek and his associates (210) observed two cases of ventricular fibrillation in dogs under cyclopropane and epinephrine injection, it is probable that ventricular fibrillation was the cause of death.

Taylor (325) in 1941 published a paper on cyclopropane anesthesia with a report of the results in 41,690 administrations.

Of particular interest to one during the period of anesthesia, if the graph in figure 67 showing the complications during 33,777 administrations, of which approximately thirty per cent showed some complication during the anesthetic period. The most frequent complication or alteration from the normal was the marked rise in blood pressure during anesthesia which was present in 10.8 per cent of all anesthesias. Cardiac arrhythmias, in 6.5 per cent of the patients, was the second most frequent abnormality observed. In figure 68 are shown the postoperative circulatory complications in the thirty-nine thousand operative and anesthetic procedures with the frequency of approximately ten per cent. It is of interest to note that during anesthesia, a marked rise in blood pressure was present in thirty-six hundred and sixty-two patients, and that the termination of the anesthesia or postoperative complications, marked fall in blood pressure without shock, occurred

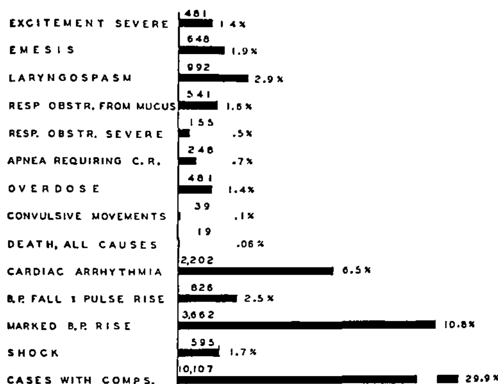


Fig. 67 (Taylor Anesthesiology, 2, 641, 1941)

in thirteen hundred and ninety-seven patients, and frank shock in three hundred and ninety-six subjects. Major respiratory complications, postoperative, were present in 1.28 per cent; minor respiratory complications in 6.6 per cent of the patients. Gastrointestinal complications were much more frequent than with any other general system and 37.6 per cent of the patients had some type of gastrointestinal complication varying from nausea on the operative day through distention and nausea and vomiting on more than the operative day. Complications involving the central nervous system all the way from headache to stupor were present in 6.4 per cent of the subjects, and genito-urinary complications were present in 11.8 per cent of the patients with mild retention accounting for ten of these 11.8 per cent. The overall mortality

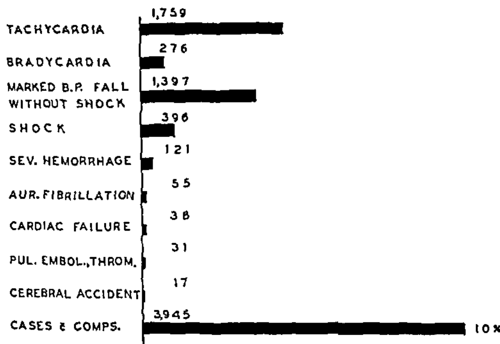


FIG 68 Taylor· Anesthesiology, 2, 641, 1941)

in this series was 2.6 per cent, and the cause of the mortality or at least the assigned cause of the mortality is shown in figure 69.

Postoperative circulatory complications are relatively infrequent following cyclopropane anesthesia. Waters and Schmidt (341) reported severe drop in pressure in 4.5 per cent of cases after cyclopropane and 2.5 to 3.0 per cent after ethylene or ether. Shock was present in 1 per cent after cyclopropane and .5 per cent after ethylene or ether. Moffitt and Mechling (217) observed shock in 5 per cent after cyclopropane, 8.7 per cent after nitrous oxide, 3.4 per cent after spinal, and 8.5 per cent after ether anesthesia in 200 major operations with each agent.

Postoperative nausea or vomiting occurred in 56 per cent after ether, 39 per cent after cyclopropane, 33 per cent after ethylene, and 23 per cent after nitrous oxide in the series of 10,638 cases

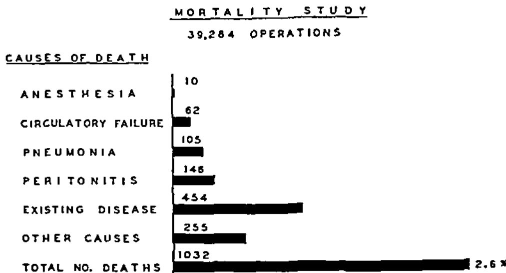


FIG. 69 (Taylor Anesthesiology, 2, 641, 1941)

studied by Waters (341), distention developed in 16.5 per cent after ether, 13.5 per cent after cyclopropane, 7 per cent after ethylene, and 3 per cent after nitrous oxide; only cyclopropane and ether were used for abdominal surgery.

Moffitt and Mechling (217) found less nausea or vomiting after cyclopropane than after ether or ethylene but more than after nitrous oxide or spinal anesthesia.

Morgan, Eaman, and Griffith (219) reported that after cesarean section under ethylene or ether, severe abdominal distention and ileus developed in 24 per cent and 7 per cent, respectively, whereas after cyclopropane severe distention was present in only 2 per cent and no ileus developed. They had 100 cases in each group.

Griffith (123) believes there is less distention in general after cyclopropane than after ethylene or ether.

Retention following cyclopropane anesthesia is not infrequent; Waters (339) found an incidence of 2 per cent after ethylene, 2.8 per cent after nitrous oxide, 5 4 per cent after ether, and 7.5 per cent after cyclopropane, he does not believe, however, that the anesthetic agent is the major factor in the postoperative distention.

Moffitt and Mechling (217) found retention in 5 per cent after ethylene, 14 per cent after nitrous oxide, 10.5 per cent after ether, 11.7 per cent after cyclopropane, and 25 per cent after spinal anesthesia. They found less nephritis, cystitis, and hematuria after cyclopropane than after the other agents.

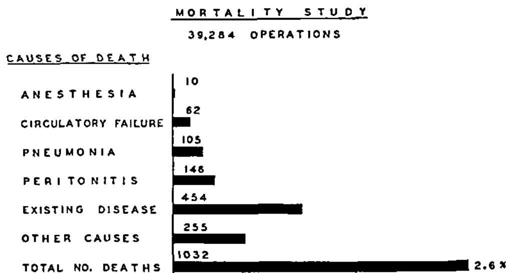


FIG 69. (Taylor. Anesthesiology, 2, 641, 1941)

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10

Indications and Contraindications for the Use of Cyclopropane

INDICATIONS FOR THE USE OF CYCLOPROPANE

Many anesthetists feel that cyclopropane and oxygen may be used in any type of patient that is to receive an inhalation anesthetic. Waters and Schmidt (341), Eversole *et al.* (96), Tidmore (336), Sword (324), Griffith (123), Houston (152), Sise *et al.* (301), and many others have reported the use of cyclopropane anesthesia for general surgery in many thousand cases in patients varying in age from 10 minutes to 98 years. The type of operative procedures covers fairly well the whole series possible except those in which cautery, x-ray, or high frequency current apparatus prevented its use.

Cyclopropane is of such potency that it can be used to produce any depth of anesthesia but yet permit the use of a high concentration of oxygen in the anesthetic mixture. It is the combination of potency, rapidity of action, lack of irritation to the respiratory tract, and high oxygen content that makes cyclopropane-oxygen of special value in certain conditions. These conditions are:

1. Short operations where relaxation is needed
2. Operations where excess oxygen is needed
   a. Due to mechanical causes
      (1) obstruction in respiratory tract
      (2) reduction in alveolar bed
   b. Increased O_2 usage
      (1) hyperthyroidism
      (2) pregnancy
   c. Anemias

have a sufficient amount of oxygen in the mixture to give adequate oxygenation.

The use of cyclopropane-oxygen in chest surgery is of great value, and several anesthetists have used it for this purpose. Rovenstine (286) reported its use in 160 thoracic surgery cases and lists its advantages for this use as follows: lack of respiratory stimulation, rapid induction and recovery, high oxygen content available, absence of irritation to the mucous membranes. Eversole and Overholt (95), in discussing the problems of anesthesia in thoracic surgery, concluded that cyclopropane-oxygen meets the needs of these patients better than any other agent or combination of agents. Knight (171) believes that cyclopropane is the anesthetic of choice for thoracic surgery.

Coryllos and Bass (69) have reported a comparative study of anesthetics in 1,370 cases of thoracic surgery. They are of the opinion that cyclopropane is an excellent agent for anesthesia in thoracic surgery with the exception of the quite frequent drop in blood pressure that is observed soon after the termination of the operative procedure. More recent studies by others have shown that this fall in pressure is due, as a rule, to inadequate ventilation during the period of anesthesia and that it can be prevented by supplementing the respiration throughout the whole operative and anesthetic procedure.

Nosworthy (236) has used cyclopropane extensively in anesthesia for chest surgery and is particularly pleased with its use as an agent to control the respiration during surgery, and he feels that it is satisfactory in all types of surgery within the chest. The ease by which the respiration is controlled during cyclopropane anesthesia is due to two factors. First, cyclopropane depresses the respiratory center from the beginning, and second, the high concentration of oxygen permitted in the anesthetic mixture makes the control of the respiratory function much easier, so that a slight wash out of the carbon dioxide will cause the respiratory effort of the patient to be inhibited.

Wiggin and Schultz (343) have reported their study on the

3. Cardiovascular disease
4. Severe operative risks

The rapid induction, adequate relaxation, and rapid recovery with cyclopropane make it an ideal agent in cases where the operative procedure is short but for which relaxation is essential. It is not quite so rapid in action as nitrous oxide or ethylene, but the relaxation and oxygenation obtainable with cyclopropane make it better than these agents.

Mann (194) has reported his observations on the nasotracheal-cyclopropane anesthesia for tonsillectomy and teeth extraction. His procedure for this use is rather complicated, but he finds it quite satisfactory. The subject is premedicated with nembutal .06 to .1 gram followed by morphine 15 mgm., hyoscine .6 mgm., then he applies a ten per cent cocaine solution to the nasopharynx by spray. Induction is by way of pentothal sodium after which the tube is inserted into the trachea by way of the nose under direct laryngoscopy and then the anesthesia continued by use of cyclopropane inhalations.

Harang (141), likewise, has used cyclopropane for oropharyngeal surgery in which the anesthetic was administered through the nasotracheal tube, and he uses cyclopropane for the anesthesia in order to do the intubation. He finds that it is quite satisfactory and the technic is rather rapid.

Our preference for induction of anesthesia where nasotracheal intubation is contemplated or desired is by the use of cyclopropane and at times the addition of a small amount of ether for a minute or two immediately before intubation. The addition of ether is desirable from two points of view. First, it depresses in part the pharyngeal and laryngeal reflexes, and second, it permits a longer period of time for the intubation. With cyclopropane alone, if the tube is not successfully passed within the first thirty seconds, the patient is apt to become too light for satisfactory intubation by the blind technic.

In cases with partial obstruction of the respiratory tract it is possible to produce anesthesia in a relatively short time and yet

(285) have shown that of eight agents used cyclopropane was the only one that did not depress or abolish respiration of the fetus when the mother was anesthetized. Griffith (123) reports the use of cyclopropane in 400 labor cases including 100 cesarean sections and reported much less postoperative disturbance following cyclopropane than after similar cases with ether. Sahler (289) has reported a series of 423 cesarean sections under different agents, 94 being with cyclopropane, and he states that the need for resuscitative measures is less when using cyclopropane and that gas pains are less frequent in these patients. Tidmore (336) reports good results with the use of cyclopropane in normal and operative obstetrics; like Sahler, he does not use premedication in cesarean sections with cyclopropane.

Karp and Richardson (166) have reported on their observations of the use of cyclopropane in obstetrics over a series of 1,392 cases. Whereas in 1937, only ten per cent of the deliveries at their institution were under cyclopropane, during the period of 1940 to 1941 approximately ninety-eight per cent of the anesthesias for obstetrical cases were cyclopropane, oxygen and helium. During the first stage of labor they provided analgesia for the expectant mother by having her breathe a mixture from a five to six-liter bag which had been filled with cyclopropane, twenty per cent, oxygen, thirty-three per cent; and helium, forty-seven per cent. They asked the subject to take three breaths of this mixture as the pain began and to hold and bear down at the end of the third breath. This provided very satisfactory pain relief during the first stage of labor. Cyclopropane-oxygen was also used for cesarean section in eighty-six patients in their series and was found to be quite satisfactory both from the fetal and maternal points of view.

Allen and Slocum (6) believe that cyclopropane-oxygen is the most satisfactory inhalation anesthetic for patients undergoing cesarean section. Their reasons for this belief is first, the rapidity with which anesthesia is induced with cyclopropane; second, that it is non-irritating; third, that the patient may be prepared and

anesthetic procedures in thoracic surgery over a series of 2,000 cases, and they believe that cyclopropane-oxygen provides the best anesthetic available for these patients.

Neff, Phillips, and Gunn (228) prefer cyclopropane and oxygen for anesthesia for the pneumonectomy in man. Their preference for cyclopropane is based in part upon the ease by which the respiration may be controlled or that apnea may be produced, and the rapidity by which one can produce the apnea and also by which the return to normal respiratory effort by the patient is produced as soon as the carbon dioxide filter is removed. Likewise, Morton (224) favors the use of cyclopropane and oxygen in those patients in whom the respiration is to be controlled. He prefers to medicate his patients with omnopon 22 mgm. plus scopolamine .4 mgm. and to induce anesthesia with pentothal sodium .5 grams or less and to carry the patient on cyclopropane and oxygen for the operative procedure. He finds that with this premedication and the pentothal injection it is easy to gain control of the respiratory function of the patient under cyclopropane anesthesia by the wash out of small amounts of carbon dioxide.

The use of cyclopropane-oxygen in patients with hyperthyroidism has a rational basis: These patients need more oxygen than the normal; this need is supplied by the excess oxygen in the mixture, the rapid induction with the relative absence of the stage of excitement or delirium is beneficial to these patients, many of whom already show some cardiac abnormalities. Sise (300) is of the opinion that cyclopropane-oxygen has advantages over the other inhalation agents in thyroid surgery. Goetsch (110) also believes that cyclopropane is of special value in thyroid cases.

The use of cyclopropane-oxygen for anesthesia during delivery, either normal or operative, is of special value (171); the woman at term uses more oxygen than normally and this is readily supplied. Also it has been shown by Snyder and Rosenfeld (307) that several of the general agents depress the fetal respiration, and in an experimental study on rabbits Rosenfeld and Snyder

cyclopropane follows:

> Cyclopropane is the best inhalation anesthetic available for vaginal deliveries because it affords the following advantages. It has a pleasant, rapid induction and emergence. It permits the use of high concentrations of oxygen and it produces no ill effects on parenchymatous structures. Its potency and lability of action afford a flexibility in its administration that can not be duplicated by any other agent Its chief disadvantages are its potential inflammability and explosiveness and occasional production of disturbance of cardiac rhythm and a tendency to produce maternal and fetal respiratory depression when anesthesia is carried deeper than the first plane of the third stage.

Apgar and her associates (11) report a very extensive and thorough analytical study on the comparison of regional and general anesthesia in obstetrics with special reference to transmission of cyclopropane across the placenta. Their report analyzed the results on 2,856 patients who were delivered vaginally and at term during the year 1955. Of these patients, 837 received regional anesthesia of which ten per cent received pudendal block or local infiltration at the epesiotomy area, forty-four per cent received sacral or lumbar epidural block, and forty-three per cent received spinal anesthesia. Of the other 2,019 receiving general anesthesia, 1,022 were anesthetized with cyclopropane. In their effort to decide which anesthetic technic was superior, they determined three different factors or values on the different groups: (1) the neonatal death over a period of twenty-eight days; (2) the time to sustain adequate respiration, using 150 seconds following the delivery as a maximum normal period; (3) their "score" or evaluation of the new born infant. This "score" is a numerical value, varying from 0 to 10 at the greatest spread, which is made up of measurements of the heart rate, respiratory effort, muscle tone, sensitivity to nasal stimulation and color. An infant having a score of ten was perfect. When neonatal death rate was compared, there were no significant differences in any of the groups. When the time to sustain respiration was determined, it was observed in the local or regional group that only 3 4 per cent needed more than 150 seconds to breathe regularly and normally, whereas with cyclopropane, 9.1

draped before anesthesia is begun, thus reducing markedly the effect of the anesthetic on the fetus; and fourth, the presence of an adequate amount of oxygen in the inspired mixture. In an effort to provide the fetus with an adequate amount of oxygen *immediately before it was removed from the uterus, they stopped* the administration of cyclopropane and oxygen at the time the uterus was opened and gave the *patient only pure* oxygen until the fetus was removed and the cord was clamped, after which the cyclopropane was added again to the inhalation mixture to provide anesthesia for the latter portion of the operative procedure. They felt that cyclopropane-oxygen was particularly valuable in patients with cardiovascular disease during the delivery period.

Allen, Weekley and Metcalf (9A) in 1957 published a paper in which they analysed their results in 1011 cesarean sections, from 1948 to 1956, with cyclopropane as the anesthetic agent. These sections were done in a hospital where over 95 per cent of the cases were private and less than 5 per cent service cases. Their procedure for anesthesia, after proper premedication with a belladonna derivative or later in the study with a barbiturate, levorphanol and scopolamine, was to induce anesthesia with just enough cyclopropane so that when the skin incision was made one minute after the intravenous injection of 6 to 12 mgm. Tubocurarine the patient might move but have no memory of painful stimuli. Respiration was assisted and upon removal of the foetus within 6 to 9 minutes after the beginning of the operation the level of anesthesia was deepened and maintained sufficient for any surgical procedure. There was *no maternal death resulting* from the anesthesia. The net infant mortality was 4.7 per cent with 2.4 per cent still birth and 2.3 per cent neonatal deaths. They feel that good results for anesthesia are directly proportioned to the care and observation the patient receives prior to operation and to precise attention during operation.

Bonica (31) has written upon obstetrical analgesia and anesthesia in general practice. A quotation from his paper upon

cyclopropane follows:

Cyclopropane is the best inhalation anesthetic available for vaginal deliveries because it affords the following advantages. It has a pleasant, rapid induction and emergence. It permits the use of high concentrations of oxygen and it produces no ill effects on parenchymatous structures. Its potency and lability of action afford a flexibility in its administration that can not be duplicated by any other agent. Its chief disadvantages are its potential inflammability and explosiveness and occasional production of disturbance of cardiac rhythm and a tendency to produce maternal and fetal respiratory depression when anesthesia is carried deeper than the first plane of the third stage.

Apgar and her associates (11) report a very extensive and thorough analytical study on the comparison of regional and general anesthesia in obstetrics with special reference to transmission of cyclopropane across the placenta. Their report analyzed the results on 2,856 patients who were delivered vaginally and at term during the year 1955. Of these patients, 837 received regional anesthesia of which ten per cent received pudendal block or local infiltration at the epesiotomy area, forty-four per cent received sacral or lumbar epidural block, and forty-three per cent received spinal anesthesia. Of the other 2,019 receiving general anesthesia, 1,022 were anesthetized with cyclopropane. In their effort to decide which anesthetic technic was superior, they determined three different factors or values on the different groups: (1) the neonatal death over a period of twenty-eight days; (2) the time to sustain adequate respiration, using 150 seconds following the delivery as a maximum normal period; (3) their "score" or evaluation of the new born infant. This "score" is a numerical value, varying from 0 to 10 at the greatest spread, which is made up of measurements of the heart rate, respiratory effort, muscle tone, sensitivity to nasal stimulation and color. An infant having a score of ten was perfect. When neonatal death rate was compared, there were no significant differences in any of the groups. When the time to sustain respiration was determined, it was observed in the local or regional group that only 3 4 per cent needed more than 150 seconds to breathe regularly and normally, whereas with cyclopropane, 9.1

per cent required over 150 seconds for adequate sustained respiration. When one compares the "score" evaluation in' the full term vaginal delivery, it is found that 5.1 per cent of the individuals delivered under regional anesthesia receive a score of 0 to 4, whereas in those delivered under cyclopropane anesthesia, 10.4 per cent receive a score of 0 to 4. In infants delivered under elective cesarean section, one per cent of those under regional anesthesia have a score of 0 to 4, whereas forty per cent of the infants delivered under cyclopropane anesthesia have a score of 0 to 4. They conclude,

> in both clinical and biochemical studies, infants born with the mother under general anesthesia, and specifically cyclopropane, were more depressed than those born with the mother under regional anesthesia. Cyclopropane is transferred rapidly to the fetus, but as used clinically in this study, equilibrium with the mother was not reached There was no biochemical evidence that cyclopropane depressed placental function This suggests that the gas exerted a direct narcotic action on the fetus, despite the absence of correlation between the blood concentration of the gas and the condition of the infant at birth

In patients with a severe anemia, where the oxygen capacity is reduced, the high concentration of oxygen used with cyclopropane should be of value in keeping the blood well oxygenated.

Hershey and Rovenstine (148) have reported upon the value of cyclopropane in the anesthetic management of patients with recent severe hemorrhage. Because of their satisfactory results obtained with cyclopropane in patients with severe hemorrhage, they carried out a study of controlled bleeding on dogs and cats to see if these animals tolerated cyclopropane anesthesia satisfactorily. They bled their animals of twenty-five to thirty per cent of the total blood volume, and in a short time thereafter, approximately one-half hour, they put the animals to sleep with cyclopropane and determined the alteration of the blood pressure, the pulse pressure, and the pulse rate during anesthesia. They concluded that the cyclopropane did not produce any undesirable effects but possibly an improvement of the circulatory system because of the fact that during anesthesia with cyclopropane the

blood pressure rose from an average of 64 to 104 mm. of mercury, the pulse pressure from an average of 8 to 44 mm., and the heart rate was reduced from 174 per minute in the dog to 71 per minute.

Regardless of the fact that cardiac irregularities are relatively frequent under cyclopropane anesthesia, several anesthetists are of the opinion that the high oxygen content and the ease of induction with cyclopropane are of such value that they prefer to use cyclopropane in the patients with serious cardiovascular lesions and other poor surgical risks. In the series of cases reported by Kurtz, Bennett, and Shapiro (175) over 50 per cent of the patients in whom cyclopropane was used had demonstrable cardiovascular pathology, whereas in the group anesthetized by other agents cardiovascular pathology was present in only 25 per cent of the cases. Eversole *et al.* (96) believe that cyclopropane-oxygen is to be preferred in patients with cardiac disease, as well as in other poor operative risks.

The marked increase in operative procedures on the cardiovascular system during the past ten to twelve years has given rise to several papers upon the anesthesia in relation to cardiac surgery. Adelman (2) in 1948 reported on anesthesia in surgery of patent ductus arteriosus on thirty patients In one child, ether was used, in nineteen cases cyclopropane was the sole agent, and in the remaining ten, cyclopropane and ether mixtures were used with cyclopropane as the primary agent. He felt that cyclopropane had its advantages in that it is rapid in induction, permits adequate oxygen in the mixture, and produces quiet unstimulated respirations in the patient. Endotracheal intubation was done only on seven patients for purposes of correcting laryngospasm, training of anesthesiology residents, and as a result of bronchiectasis in one individual. He felt that intubation was not imperative and that a tight-fitting mask was quite satisfactory in the majority of the patients in the production of adequate gaseous exchange by artificial respiration or supplementation of the respiration in the patient.

McQuiston (208) has reported a study on the anesthesia in

cardiac surgery in 362 cases. In this study he concluded that cyclopropane-oxygen is the agent to be favored in most cases for the following reasons: First, that cyclopropane is potent and pleasant to take; second, that it is absorbed rapidly and equally rapidly eliminated; third, that it is not irritating to the upper respiratory tract and the trachea of the individual.

Rind, Helliwell, and Hutton (267) have reported on the use of endotracheal-cyclopropane anesthesia for operations for the relief of congenital pulmonary stenosis. They prefer to use cyclopropane for induction and intubate all their patients and maintain them on cyclopropane and oxygen during the operative procedure.

Dripps and his associates (90) terminate their discussion of cyclopropane anesthesia with the following paragraph:

> Cyclopropane remains a controversial anesthetic. We like its controlability, potency and patient acceptance. We rely on it frequently for the anesthetic management of critically ill patients There is increasing evidence in man of the safety of the drug and we believe that it merits more widespread use

CONTRAINDICATIONS FOR THE USE OF CYCLOPROPANE

Cyclopropane for surgical anesthesia is contraindicated in two instances. first, where cautery, x-ray, or other electrical apparatus is necessary for carrying out the operative procedure; and second, where it is anticipated that epinephrine HCl will have to be employed.

Due to the fact that cyclopropane-air or cyclopropane-oxygen mixtures are explosive over the range used in anesthesia, it should not be used for anesthesia where there is any reason to expect that a possible source of ignition of the anesthetic mixture may be used. A full discussion of this point will be given in Chapter 12.

The careful experimental studies of Meek *et al.* (210) and Orth *et al.* (246) on the effect of anesthesia upon the irritability of the automatic tissues of the heart have shown that cyclopropane increases the irritability more than chloroform or ether. They have shown conclusively that the injection of epinephrine HCl

in relatively small amounts, in dogs under cyclopropane leads to the development of severe cardiac irregularities in all dogs and to ventricular fibrillation in a fair number of the dogs. There have been clinical observations with the use of epinephrine HCl in patients under cyclopropane which, although not controlled by electrocardiographic records, would lead one to believe that man may react the same way as the dog in this relation. Waters (339) reported one case which apparently died of ventricular fibrillation after the intracardiac injection of epinephrine HCl. Guedel and Knoefel (133) in their discussion of fibrillation under anesthesia reported a patient who died under cyclopropane from fibrillation and stated that the use of epinephrine to control localized bleeding should be condemned. They also stated that since morphine does not depress the activity of the adrenals, barbiturates which do depress the activity of the sympathetic system might protect against the development of cardiac fibrillation during anesthesia.

The evidence available at the present time, both experimental and clinical, indicates that epinephrine HCl and certain other sympathomimetic amines (1, 133, 210, 243) should not be used during cyclopropane anesthesia.

Although it had been known for some time, in the experimental animal at least, that the pituitary solution would cause a constriction of the coronary vessels and produce fall in blood pressure with cardiac arrhythmias, it remained for Adelman and Lennon (3) in 1941 to relate pituitary shock with cyclopropane anesthesia. They published at that time a paper in which they reported seven cases of pituitary shock occurring during anesthesia.

Behnoff (16) in 1944 reported two deaths as the result of the simultaneous use of pituitary and cyclopropane, one in which the death was ascribed to bronchial constriction and asphyxiation, the second resulting from cardiovascular shock with the patient developing a marked tachycardia with hypotension and sudden death.

Greene (114) in 1942 in a study on the posterior pituitary extracts in anesthesiology reported that in one individual receiving

cardiac surgery in 362 cases. In this study he concluded that cyclopropane-oxygen is the agent to be favored in most cases for the following reasons: First, that cyclopropane is potent and pleasant to take; second, that it is absorbed rapidly and equally rapidly eliminated; third, that it is not irritating to the upper respiratory tract and the trachea of the individual.

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anesthesia, the less frequent were the arrhythmias. Knowing, however, of the specie variation on the effect of drugs, they cautioned on the transfer of this protective effect of general anesthetics against the cardiac arrhythmias from the dog over to man and waited until a study on man had been concluded before further comments.

Morris and his associates (221) reported in 1952 a study on the comparison of effect of pituitrin, pitocin, and ergonovine on cardiac rhythm during anesthesia for parturition. In a series of twelve patients under cyclopropane anesthesia, the administration of pitocin resulted in arrhythmias of ventricular origin in only one subject, whereas in twenty-six of forty-four patients receiving pituitrin, ventricular arrhythmias were observed. They believe that it is best to give an oxytocic in labor other than the pituitrin preparation.

three units of pituitary solution during cyclopropane anesthesia, marked cardiac arrhythmias were present for some thirty minutes and hypertension of a very severe degree developed, but the patient eventually returned to normal.

Likewise, Burstein (52) in a study on the clinical observations of some systemic effects of pitressin reported that cardiac arrhythmias as a result of coronary constriction were frequently observed in the animal and that this may be prevented by the preliminary injection of ephedrine; he suggested that ephedrine be used as a therapeutic or prophylactic agent against cardiac arrhythmias due to oxygen lack in the myocardium produced by pitressin.

Lesser and Eason (183) reported that cardiac arrest under anesthesia resulted from the intravenous injection of pitocin. They feel that one should be cautious about the use of pituitary solutions, either pitressin or pitocin, during cyclopropane anesthesia.

Parsloe *et al.* (249), in a series of eighty-four experiments upon twenty-six dogs, determined the effect of the injection of pituitrin, 1 unit per kilo, on dogs under chloretone, spinal anesthesia, ether, chloroform and nembutal anesthesia; and with cyclopropane anesthesia the dose was one unit of pituitrin per kilo, one unit of pitressin per kilo or two units of pitocin per kilo; and in thirteen unanesthetized dogs the dose was one unit of pituitrin per kilo. In thirteen of fourteen experiments in which pituitrin was injected in the unanesthetized animals, cardiac arrhythmias developed. In only two of ten experiments under cyclopropane were arrhythmias observed with pitocin. In only eight of thirty-eight experiments under cyclopropane were arrhythmias observed upon injection of pituitrin. In only one of three experiments under chloroform were arrhythmias observed, whereas in nine of nine experiments under spinal, cardiac arrhythmias were present. They felt that this laboratory study indicated that the animal under anesthesia was less apt to develop cardiac arrhythmias than the animal in the awakened state and that the deeper the

11

The Relaxing Agents

In a discussion of the pharmacology of the relaxing agents, it is of interest to look over briefly a few of the earlier observations on curare, both in the laboratory and in the clinic, and then to follow with a discussion of the events of the ten-year period of 1935–1944 which led to the very widespread use of those agents in various fields of medicine. First, Pelouse and Bernard, 1850 (251), Kolliker, 1856 (174), and Bernard, 1856 (21), reported studies on the frog which showed that the site of action of curare in producing paralysis of the muscle was at the junction of the nerve and muscle. Demme, 1872 (83), treated several patients with tetanus with curare and found that the severity of the convulsions was reduced.

Pal, 1900 (248), showed that eserine or physostigmine was a pharmacological antagonist to curare. Boehm, 1889–1920, (28) isolated from various samples of crude curare several relatively pure chemical substances which would paralyze skeletal muscle; it was one of these relatively pure preparations that Lawen (178) of Leipzig used in 1912 in man to reduce the amount of the inhalation anesthetic necessary to close the abdomen. He thought that the postoperative respiratory complications following anesthesia and surgery were due to the depression of the respiratory center by the deep anesthesia needed for closure of the abdomen, and recommended the use of curare or local anesthetic to aid general anesthesia.

Thus, at least twenty-five years before serious application of the relaxing agents to clinical problems was made, it was known that

1. Curare produced paralysis by action of the M-N junction.
2. Curare had been used to control convulsions in tetanus.

to acetylcholine was released, and that the close intra-arterial injection of acetylcholine would produce a contraction of the muscle; also that after curarization of an animal the stimulation of the nerve released acetylcholine, and that the use of physostigmine in such a curarized preparation would cause the muscle to contract after nerve stimulation. These studies of Dale *et al.* showed:

First: That acetylcholine was the chemical mediator of nerve impulse to skeletal muscle.

Second: That curarine did not prevent the elaboration of acetylcholine but blocked its action upon the muscle.

Third: That by giving physostigmine, a substance that would permit a build up of a higher concentration of acetylcholine at the motor end plates, the curarine block could be broken. This gave rise to the theory that curarine produced its effects by competition with acetylcholine for certain specific receptors.

Thus, the work by Dale and his associates formed the ground work for an understanding of nerve-muscle physiology and explained how curare might work and how an antagonist terminated the action of curare.

2. Establishment of structure of d-tubo curarine—Although the studies of the pharmacological or physiological action of curare began as early as 1811 by Brodie (41) and by Pelouse and Bernard in 1852, attempts at identifying the active principle were not extensive until the studies of Boehm, 1889–1920 (28), showed that the various curare preparations contained a quaternary N unit. It was the studies of King (168) in England that established the chemical formula of the active agent in crude curare, and it was he who suggested that the source of the active substance in crude curare was the plant chondodendron tomestosum. Later Wintersteiner and Dutcher (345), 1942, proved King's formula (except for the placement of one methyl group) by studies of curare from a known plant source (Ch. tomestosum).

3. Need for relaxing agent—During the period of 1935–1944 there were several developments in medicine and anesthesia that gave rise to a need for relaxing agents, and these were:

3. Physostigmine was a pharmacological antagonist.
4. "Curare" had been used in surgery to reduce tone of skeletal muscle.

Let us now look over the period of 1935–1944 to see what *conditions were present to bring about this widespread interest* in and use of muscle relaxing agents as aids to medicine, particularly anesthesia. At least four separate developments during the ten-year period led to the final interest in and use of the relaxing agent·

(1) Studies in the mechanism of nerve-muscle action by Brown, Dale, and Feldberg, 1936–1938.
(2) Isolation and chemical characterization of d-tubo curarine by King, 1935; Wintersteiner, 1942.
(3) Need for muscle relaxation in diagnostic and therapeutic procedures as well as aids in relaxation with new anesthetic agents and technic: endotracheal intubation, cyclopropane, thiopental, nitrous oxide.
(4) Introduction of a standardized preparation of curare by Bennett, 1939, Gill, 1938–1939; McIntyre, Holaday.

I wish to make a few comments about each of these four factors before going on into a discussion of the pharmacology of the various agents in current use to produce muscle relaxation.

1. Nerve-muscle function—Until the analytical work of Dale and his associates (42), there were two theories on the mechanism of transfer of the nerve impulse across the neuro-myal junction to the skeletal muscle, i.e., electrical and humoral. It had long been known that the stimulation of a motor nerve and its muscle was associated with an electric impulse, and that the muscle contraction from nerve stimulation could be reduced or prevented by the use of certain drugs, i.e , physostigmine and curare, at a time when both the nerve and the muscle separately were susceptible to electric stimuli, thus showing that the mechanism of the transfer of stimuli from the nerve to the muscle was inhibited. Further work by Dale *et al.* (80) showed that during the stimulation of a nerve-muscle preparation a substance similar in action

to acetylcholine was released, and that the close intra-arterial injection of acetylcholine would produce a contraction of the muscle; also that after curarization of an animal the stimulation of the nerve released acetylcholine, and that the use of physostigmine in such a curarized preparation would cause the muscle to contract after nerve stimulation. These studies of Dale *et al.* showed:

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In the second edition of 1955, some twenty pages are used discuss curare and those substances which have been develop as the result of the attempts to prepare more satisfactory a safer substitutes for d-tubo curarine. Likewise in another te: "Pharmacology in Medicine", edited by Drill (88) in 19 McIntyre devotes an entire chapter of fifteen pages to a ve concise discussion of this subject.

There are two mechanisms by which the effect of nerve stin lations is blocked:

1. Prevention of depolarization.
2. Prolongation of depolarization.

Zamis (350) in a review on the "Transmission and Block Motor End Plates" defines the differential characteristics of t two types of block that may occur.

1. Block by competition for acetylcholine receptors by d-tu curarine.
   a. Block is not preceded by potentiation or fasciculation
   b. Muscle will not maintain a tetanus.
   c. Block is antagonized by eserine.
   d. Drugs producing block by competition will not prod contracture in the denervated muscle.
2. Block by depolarization, as one gets by acetylcholine a eserine or succinylcholine Cl, is characterized by the foll ing:
   a. Block is preceded by potentiation and fasciculat (particularly noted with succinylcholine).
   b. Tetanus is maintained.
   c. Block is not antagonized by eserine.
   d. Contracture with denervated muscle.

Regardless of the mechanism by which the block is produ by the different drugs, there is a constant order in which various muscle groups are paralyzed in man, and this is:

a. Extrinsic muscles of the eye.
b. Facial muscles.
c. Muscles of the neck.

a. The use of shock therapy in psychiatric diseases (a drug was needed to reduce the intensity of muscle contraction so as to prevent fractures).

b. The widespread use of cyclopropane and thiopental, neither of which produce adequate relaxation of abdominal muscles for upper abdominal surgery.

c. The increased use of endotracheal intubation as an aid in anesthesia. Non-traumatic intubation, under agents other than ether, are much more easily done with a relaxing agent supplement than with pentothal or cyclopropane alone.

d. Laryngoscopy and bronchoscopy are much more easily carried out if a relaxing agent is used.

4. *Introduction of a standardized* preparation—*In 1938–1939,* Gill (108, 109) collected samples of curare and plants in South America and brought some to McIntyre at the University of Nebraska where he studied the pharmacology of them. Holaday (337) prepared a biologically standardized solution which Bennett, a psychiatrist, used successfully in patients in preventing fractures as a result of electroshock therapy. Three years later (1942) Griffith and Johnson (127) using a preparation, intocostrin (Squibb), first reported its use in patients anesthetized with cyclopropane.

These four developments during the period of 1935–1944 have led to the widespread interest in the use of relaxing agents.

In order that one may appreciate the advance in the interest in and use of the drugs to be discussed, one need only note the space and content of this subject in the first and second edition of the text, "The Pharmacological Basis of Therapeutics", by Goodman and Gilman (112) published in 1941 and in 1955. In the first edition a total of less than two pages is devoted to the curare group, with these few lines as the opening and closing sentences under the heading of clinical use: "Curare and its alkaloids have no valid well-established uses. Curare is used in the laboratory *to produce immobility of animals without central* nervous system paralysis but does not produce anesthesia."

carbon dioxide elimination, it is necessary for the anesthetist to aid the patient's respiratory effort.

With these preliminary comments back of us we will proceed with a discussion of the various drugs in use for the production of relaxation.

In figures 70 and 71 are shown the structural formulae of seven of the drugs used to produce relaxation. All of these drugs have something in common either from a physical or a chemical point of view. Five of the seven compounds have quaternary nitrogens separated by approximately fourteen angstrom units, and all of the compounds have a basic nitrogen, either tertiary or quaternary, in their molecule.

The drugs may be divided into two groups according to the mechanism by which they produce the block.

Block by competition with acetylcholine for receptors: (1) d-Tubo curarine, (2) Dimethyl-d-tubo curarine, (3) Flaxedil, (4) Laudolissin, (5) Mytolon.

Block by production and maintenance of depolarization: (1) Decamethonium bromide, (2) Succinylcholine chloride.

DRUGS PRODUCING BLOCK BY COMPETITION

Curare or D-*tubo curarine chloride*

Source. The source of crude curare in the past has been that of various species of the strychnos toxifera, strichnos costelani, and chondrodendron tomentosum.

Chemistry. The studies by Boehm, King, Gill, Wintersteiner, and Dutcher in relation to the isolation and identification of the active ingredient of crude curare, d-tubo curarine, have been discussed above.

Since 1948, most of the curare preparations are made from pure d-tubo curarine, and some of these are still bioassayed because there may be isomers of the d-tubo curarine present.

Absorption and excretion. d-Tubo curarine produces its typical effect when given subcutaneously, intramuscularly, or intra-

d. Muscles of extremities and trunk.
e. Muscles of the abdomen and thorax.
f. Diaphragm.

Although the muscles of the diaphragm are the last to become blocked, most students of the subject are of one opinion that in any patient in whom the desired relaxing effect is present, the muscles of respiration, although still functioning, are sufficiently weakened that for adequate gaseous exchange, particularly

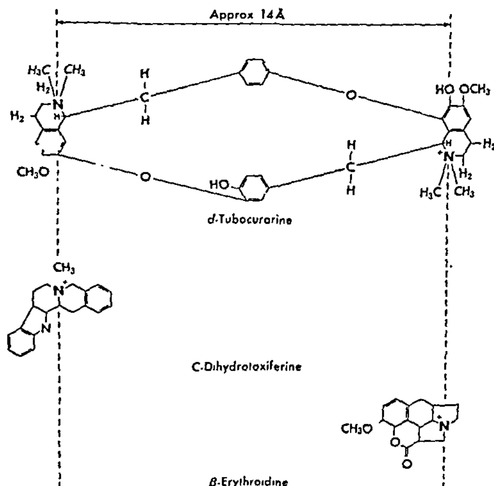


FIG. 70 Structure of naturally occurring curareform compounds (from Drill: Pharmacology in Medicine, 2nd edition, Copyright 1958 McGraw Hill Book Co, Inc.)

venously but is relatively harmless when taken by mouth. It is excreted in part by the kidneys as is shown by the following things: First, it was shown early that urine elaborated in an animal under curare would in turn produce curarization when given to a second animal. Second, Marsh (196) in 1952 published his studies on the distribution, metabolism, and excretion of d-tubo curarine chloride in man and in animals and showed that there was a significant amount of the d-tubo curarine excreted in the urine. Third, Kalow (165) in 1953 was able to recover approximately thirty per cent of a given dose in the urine of man.

Effect on the central nervous system. Hartridge and West (145) in 1931 published their reports on the effect of curare in the abolition of parathyroid tetany in dogs. They thought this improvement in the tetany was due to a central nervous system effect or action of curare.

Harris and his associates (143) in studying the effect of curare in patients undergoing metrazol convulsive therapy were unable to observe any alterations in the electroencephalographic record during the peak action of curare as contrasted to that in the control state. Likewise, Smith and his associates (305) were unable to observe any central nervous system effects in the human subject when that individual was given as much as two and one-half times the total paralyzing dose of curare.

Ellis, Morgan, and DeBeer (91) in 1953, in studies on the dog and cat diaphragm and gastrocnemius muscle, showed that the peripheral neuro-myal function returned before the central nervous system respiratory center became active. So at least in the cat and the dog there is a central nervous system effect of curare when given in large doses.

Effect on the autonomic nervous system. Langley (177) in 1918 used curare as a laboratory tool in establishing the pathways and ganglia involved in the autonomic nervous system. Luco and Mesa (191) in their studies showed that the full skeletal muscle paralyzing dose would also block the transmission of the impulses from the preganglionic to the postganglionic fiber. They

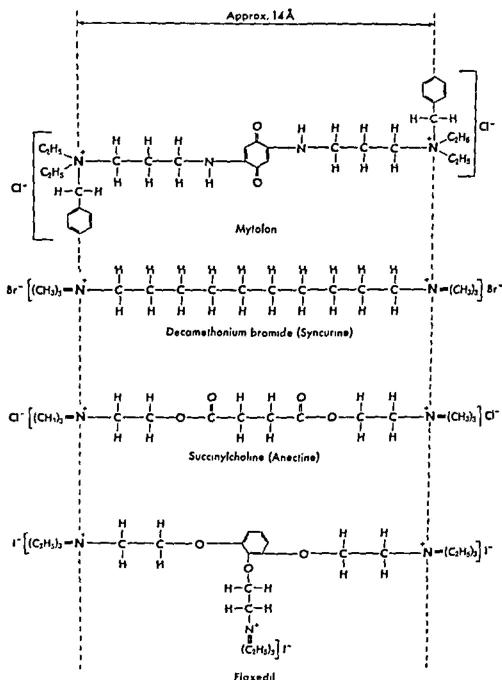


FIG. 71 Structure of synthetic curareform compounds. (from Drill. Pharmacology in Medicine, 2nd edition, Copyright 1958, McGraw Hill Book Co, Inc.)

marked similarity between the effect of curare and histamine upon the bronchial tree and upon the vascular bed. He observed that both d-tubo curarine and intocostrin may produce a release of histamine.

Clinical studies. Although Demme in 1872 had used crude curare to help in the control of the convulsions and spasticity of muscle in the therapy of the patients with tetanus, and although Lawen (178) had used a purified curare preparation to produce relaxation of the abdominal muscles for closure of the abdomen in laparotomies and suggested that it be used to reduce the frequency of postoperative pulmonary complications following abdominal operations, it remained for Bennett (18) and his associates at the University of Nebraska in 1939 to start the use of relaxing agents in medicine on a rapid way. Bennett was interested in the reduction of the frequency of fractures in patients undergoing electric shock therapy for psychiatric disorders. The frequency was approximately 28 per cent in fully treated patients. At that time, McIntyre (205) and his associates in the Department of Physiology and Pharmacology were studying in the laboratory curare and extracts from the plant chondrodendron tomentosum that were brought back by Gill from South America and investigated at Squibbs and at the University of Nebraska. Upon having available, therefore, a biologically assayed and standardized preparation of curare and a need for the relaxing agents in patients, Bennett was able to reduce the frequency of fractures from 28 per cent to approximately 5 per cent, and his studies also showed that curare could be safely administered.

In 1942, Griffith and Johnson (127) had the opportunity of using intocostrin in patients during cyclopropane anesthesia, and they reported upon their use of this substance in twenty-five patients. As a result of this study and publication, the use of curare in anesthesia throughout this country was quite rapidly spread and soon many reports covering hundreds of cases of the use of intocostrin had been published. Cullen (77, 78) was among

also showed that the full paralyzing dose had a marked effect on the conduction of the impulse from the vagus to the myocardium. They also showed that as much as fourteen times the full paralyzing dose of curare had no effect upon the transfer of impulse from the postganglionic sympathetic fiber to the effector organ. Thus, in general, one may say that curare or d-tubo curarine blocks the transfer of impulses *in the autonomic nervous system where* acetylcholine is a chemical mediator of that transfer. Harris and his associates (143) have shown that there is no effect upon the electrocardiogram of the patient under curare medication.

Effects on the skeletal muscle. As mentioned earlier, Pelouse and Bernard (251) in 1850 first showed that the site of action of curare in producing paralysis was at the junction of the nerve and the muscle. Brinkman and Ruiter (39) in 1925 were first to show that there was an acetylcholine-like substance released from the frog muscle upon stimulation of the sciatic nerve both before and after the application of curare. Brown, Dale, and Feldberg (42) in 1936 made extensive studies on the mechanism of transfer of impulse from the nerve to the muscle and found that a substance similar to acetylcholine was liberated both in the normal nerve muscle preparation and in the preparation after the administration of curare. They also showed that the intra-arterial injection of acetylcholine would produce a contraction identical to that of nerve stimulation, and that following the administration of curare the intra-arterial injection was ineffective.

Pal (248) in 1900 and later Briscoe (40) in 1936 showed the antagonism between eserine and curare, and Briscoe showed that the patient with myasthenia gravis was excessively sensitive to curare and that eserine was of help with these patients that might have had curare.

Effect on smooth muscle. The effect of curare and d-tubo curarine upon the smooth muscles of the bronchi and of the arteries is of the greatest interest because in certain instances there is a constriction or contraction of the bronchial smooth muscles.

Landmesser (176) in 1948 in his studies on dogs showed a very

marked similarity between the effect of curare and histamine upon the bronchial tree and upon the vascular bed. He observed that both d-tubo curarine and intocostrin may produce a release of histamine.

Clinical studies. Although Demme in 1872 had used crude curare to help in the control of the convulsions and spasticity of muscle in the therapy of the patients with tetanus, and although Lawen (178) had used a purified curare preparation to produce relaxation of the abdominal muscles for closure of the abdomen in laparotomies and suggested that it be used to reduce the frequency of postoperative pulmonary complications following abdominal operations, it remained for Bennett (18) and his associates at the University of Nebraska in 1939 to start the use of relaxing agents in medicine on a rapid way. Bennett was interested in the reduction of the frequency of fractures in patients undergoing electric shock therapy for psychiatric disorders. The frequency was approximately 28 per cent in fully treated patients. At that time, McIntyre (205) and his associates in the Department of Physiology and Pharmacology were studying in the laboratory curare and extracts from the plant chondrodendron tomentosum that were brought back by Gill from South America and investigated at Squibbs and at the University of Nebraska. Upon having available, therefore, a biologically assayed and standardized preparation of curare and a need for the relaxing agents in patients, Bennett was able to reduce the frequency of fractures from 28 per cent to approximately 5 per cent, and his studies also showed that curare could be safely administered.

In 1942, Griffith and Johnson (127) had the opportunity of using intocostrin in patients during cyclopropane anesthesia, and they reported upon their use of this substance in twenty-five patients. As a result of this study and publication, the use of curare in anesthesia throughout this country was quite rapidly spread and soon many reports covering hundreds of cases of the use of intocostrin had been published. Cullen (77, 78) was among

the earlier anesthesiologists to report extensive series of patients in whom curare or intocostrin was used to produce relaxation. It was noted early in the combined use of curare and ether that much less curare was needed to produce relaxation than was necessary when curare was combined with cyclopropane or with pentothal. Approximately one-third of the dose was necessary. Auer and Meltzer (13) in 1914 made a study in which they observed that ether had a marked curare-like effect upon the skeletal muscle. In 1945, Gross and Cullen (129), after the experiences of Cullen with curare in the clinic, made a study on the effect of various anesthetic agents in relation to possible curareform activity, and they found that ether had a marked curare-like action. When ether is administered, much less curare is necessary than with other agents.

Recent studies by Cullen and his associates (341a) on the effect of different anesthetic agents alone and in combination with d-tubo curarine have shown in the rabbit under cyclopropane anesthesia that with a single shock stimulus to the nerve the muscle contraction is markedly increased over the control, and that upon the addition of d-tubo curarine to the rabbit during cyclopropane anesthesia the contraction is rapidly reduced to a minimum. Upon awakening from the cyclopropane anesthesia a subsequent dose of d-tubo curarine has no effect upon the contraction resulting from a single shock stimulus but reduces that following a tetanic stimulus as shown in figure 72.

Sabawalla and Dillon (288a), in studies on the effect of cyclopropane alone and with d-tubo curarine on the contraction of human intercostal muscle produced by indirect and direct stimulation, have observed that when the muscle is treated with a 25 per cent concentration of cyclopropane, there is a marked inotropic effect, but that if 50 per cent concentration of cyclopropane is used, there is an irreversible block produced at the myoneural junction or else the function of the nerve fiber is destroyed as shown in figure 73.

When the preparation is treated with d-tubo curarine so that the contraction resulting from nerve stimulation is reduced (20

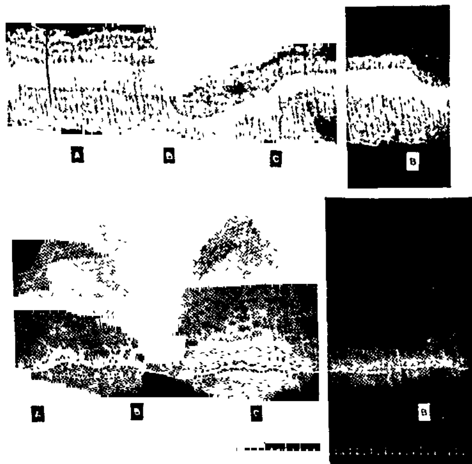


FIG. 72 The effects of cyclopropane and curare Top tracing, tetanic stimulation, bottom tracing, single shock stimulation (A) Beginning of anesthesia with 25 per cent cyclopropane (B) Curare, 50 mgm /kgm (top record); 100 mgm /kgm. (bottom record) (C) Anesthesia discontinued Curare administration in right tracing one hour following that in left tracing (After Watland, Long, Pettinger, and Cullen Anesthesiology, 18, 883, 1957.)

per cent block), cyclopropane produces a further depression of the contraction following nerve stimulation, but the positive inotropic effect with direct stimulation is the same as in the non-d-tubo curarine treated nerve muscle. Also, as soon as the cyclopropane is removed from the system, the contraction resulting from the nerve stimulation increases as shown in figure 74

In both rabbit and human muscle, cyclopropane has a positive

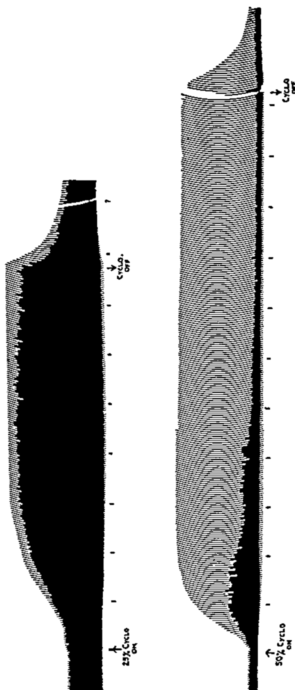


FIG. 73. The effect of cyclopropane upon human intercostal muscle. Direct and indirect single shock stimuli. Time marker 5 minutes. (Personal communication from Sabawalla and Dillon (288a).)

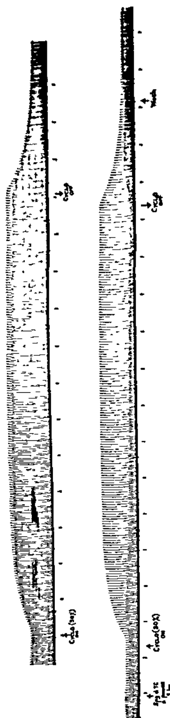


FIG 74 The effect of cyclopropane upon human intercostal muscle (top record). The additive effect of cyclopropane and d-tubo curarine (bottom record). The nerve muscle was prepared for one hour with 5 mgm. curare to give a 20 per cent block before cyclopropane added Time marker 5 minutes. (Personal communication from Sabawalla and Dillon (288a).)

inotropic effect when the muscle is stimulated indirectly or directly with a single shock stimulus. Upon the addition of d-tubo curarine, cyclopropane potentiates the effect of the neuromuscular blockade but still produces a positive inotropic effect in human muscle upon direct stimulation. A satisfactory explanation of these findings is not available at the present time.

Dimethyl-D-tubo Curarine Bromide

The dimethyl-d-tubo curarine bromide is prepared by replacing a hydrogen on two of the hydroxyl groups with the methyl radicle producing the dimethyl ether of d-tubo curarine. This product has an action identical qualitatively to that of the parent substance d-tubo curarine chloride. However, due to the dimethylization, the new compound is approximately two to three times more potent than the parent substance.

Gallamine Triethyl Iodide (Flaxedil)

Chemistry. This substance was synthesized by Bovet (36) in 1947, and in 1949 Bovet, Depierre and their associates (37) reported on its curarizing action, and also they observed that the action of this substance was antagonized or inhibited by eserine or physostigmine

Central nervous system effect. With the ordinary therapeutic dose, there are no central nervous system effects produced by the use of gallamine triethyl iodide (73, 164).

Autonomic nervous system. Transmission of impulses through the autonomic ganglia is inhibited by the application of gallamine triethyl iodide as it is by d-tubo curarine. From a clinical point of view, the most marked effect on this system is that of the increase in heart rate which is routinely observed following the administration of a partial or a completely paralyzing dose of this drug.

Skeletal muscle. Gallamine triethyl iodide produces its paralytic effect by competitive block against acetylcholine in the normal nerve muscle position The effect therefore of gallamine

triethyl iodide can be terminated or antagonized by the injection of eserine or physostigmine or prostigmine.

Clinical studies. This drug was first used and the use reported in man by Wilson and Gordon (344) in 1949. In 1950, Mushin *et al.* (227) found that a dose of 1 mgm. per kilo is sufficient to produce complete relaxation in the average human subject. They also reported that a dose of this size could be completely antagonized by the intravenous injection of prostigmine. Marbury and his associates (195), in their study in 1951 on the effect of various doses of relaxing agents upon the respiratory volume, found that the maximum effect following the intravenous injection of gallamine triethyl iodide occurred in three to four minutes with a complete recovery in twenty to twenty-five minutes.

Excretion. Thirty to eighty per cent of the injected dose of this drug is excreted unchanged in the urine.

Laudolissin

Chemistry. This substance was synthesized in 1949 by Collier and Taylor (66). It consists of two molecules of papaverine joined through the nitrogen atoms by $(CH_2)_{10}$.

Clinical studies. Collier and Macauley (65) published the first pharmacological study and clinical study on laudolissin in 1952. They found it to be long acting and that it produces relaxation by competitive block with acetylcholine. Wyant and Sadove (349) reported the use of this drug in one hundred cases in 1954. They found it to be slow in onset of action, the duration of action excessively long, and also that it is additive with the curare effect of ether. They reported that edrophonium was effective in shortening or terminating the action of this substance in man.

Benzoquinonium (Mytolon)

This substance was prepared by Cavallito, Soria, and Hoppe (60) in 1950. It is a relaxing agent that seems to have effect both

from the point of view as a competitive block agent and also one that produces prolonged depolarization. Its use has been reported by Arrowood (12) in the production of muscular relaxation in 1951 and also by Gordon (113) in 1953. It produces in the human three things that make its use very unsatisfactory. First, after its administration, the patient secretes a very viscid secretion in the mouth and in the trachea. Second, it produces a bradycardia. Third, this bradycardia may be of such an extent that hypotension may result from the slow pulse. Gordon feels that this substance does not appear to be of much value in general use for production of relaxation. There may, however, be on rare occasions special advantages in its use.

DRUGS PRODUCING DEPOLARIZATION

Decamethonium Bromide

Chemistry. In 1948, Barlow and Ing (14) reported their study on the curare-like action of polymethylene bisquaternary ammonium salts. In this series of compounds, the one having ten carbons between the two nitrogens was found to be the most effective in the production of relaxation of muscle in the animal.

Effect upon the nervous system. Ellis, Morgan, and DeBeer (91) in 1953 found depression of the respiratory center after the administration of decamethonium in the dog following the return of the peripheral nerve muscle unit to normal function. They felt that there is some central nervous system effect with this drug. Thesleff (331) in 1952 reported that decamethonium or syncurine had practically no effect upon the transmission of impulses through the ganglia. In fact, it required somewhere between sixty-five and one hundred full paralyzing doses to produce any effect upon ganglionic transmission.

Skeletal muscle. Decamethonium produces its relaxation by causing a depolarization of the nerve muscle area and a prolongation of this depolarization.

Clinical use. Organe (241) in 1949 reported the use of this drug

in man. Its action is characterized by the rapid onset of relaxation within a period of three to four minutes after its intravenous administration and a moderately long duration of effect in the range of fifteen to twenty minutes. Spencer and Coakley (309) in an extensive study of this drug in 2,400 cases reported its satisfactory use for many anesthesiological problems. They were particularly pleased by its relative rapid onset of action and its shorter duration of effect than with d-tubo curarine. There was no evidence of histamine release or histamine production by the administration of this drug.

A very complete report of pharmacological studies of decamethonium and other members of this series has been made by Paton and Zamis (250) in 1952.

Succinylcholine Chloride

Chemistry. This substance was originally prepared and studied from the pharmacological point of view by Hunt and Taveau (154) in 1906 as one member of the series of cholines that they were investigating upon the experimental animal. They did not observe the paralytic effect of this substance on their animal; it was not reinvestigated until the studies by Bovet in 1949, and DeBeer and his associates in 1949. Both groups were studying the effect of choline-type compounds on the animal.

Absorption and excretion. This substance, due to its very rapid onset of action and short duration, is best given by the intravenous route. It is hydrolyzed in two stages in the body. First, the succinyldicholine is hydrolyzed to succinylmonocholine very rapidly; and second, the succinylmonocholine is hydrolyzed slowly to succinic acid and to choline. Approximately three per cent of the succinylcholine is excreted in the urine, and somewhere between six and ten per cent of the succinylmonocholine is excreted in the urine according to studies by Foldes *et al.* (102). The human body is able to take care of or hydrolyze a very large amount of this drug in a relatively short period of time. Martin, Nowill, and Stephen (202) in their study of this drug

found in ten subjects after the intravenous administration of 1,000 mgm. of this drug in a period of ten minutes that apnea lasted from eight to forty minutes with twenty minutes as an average. In approximately ten to twelve per cent of patients that receive a large dose of succinylcholine over a relatively long period of time, there is a prolongation of the respiratory depressant effect to a much greater extent than one would expect. Martin, Nowill, and Stephen (202), as well as Davis, Ellis and their associates (81), have written upon this subject. Neither group has found a satisfactory explanation of this occasional prolongation in the duration of the effect, nor has either of the groups been able to find a mechanism by which this effect may be terminated.

The nervous system. DeBeer and his associates (82) found upon the study of the central nervous system effect of succinylcholine that there persisted a respiratory center depression after the termination of the peripheral effect of succinylcholine on the nerve muscle unit. Thesleff (331), in his studies upon the effect of succinylcholine on transfer of impulses through the ganglia, found that with this drug approximately 650 to 700 times the total paralyzing dose was necessary before there was an interruption of transfer of impulse from the preganglionic to the postganglionic fiber.

Skeletal muscle. The paralyzing action by succinylcholine upon the skeletal muscle is by way of the production of a depolarization and a prolongation of the polarized state. All the characteristics of this type of block as defined by Zamis earlier in this chapter are present upon the administration of this drug. Of *particular easy observation is that of the fasciculation* which occurs almost routinely when a paralyzing dose of succinylcholine is administered intravenously in a shorter period than thirty seconds. In a paper by Espinoza and Artusio (92), they reported that the muscle function returned to 80 per cent of normal within ten minutes after an initial paralyzing dose. They are of the opinion that the respiratory muscle depressing dose is

approximately the same as for other skeletal muscle, and they conclude that it does not seem likely that there will be a relaxing agent that spares the function of the respiratory muscle. In contrast to this opinion, however, Thesleff (329), in his studies on the muscle relaxant action of succinylcholine iodide in man, found that .2 mgm. per kilo produced 100 per cent paralysis in the muscles of the extremities, whereas .2 mgm. per kilo only produced 60 per cent paralysis of the intercostal and diaphragmatic muscles.

Clinical use. Soon after the chemical and pharmacological reinvestigation of succinylcholine by Bovet and his associates (37) and Phillips (255), the clinical use of this agent was reported from Sweden by Thesleff (330) in 1952, by Scurr (294) in Britain in 1951, by Bourne, Collier, and Somers (33) in 1952, by Foldes and McNall (101), and by Little, Hampton, and Grosskreutz (187) in the United States in 1952. Since that time, the widespread use of succinylcholine as an adjunct to general anesthetic agents in the production of relaxation of the skeletal muscles in the absence of very deep anesthesia has become quite marked. Martin and her associates (202), Davis and his associates (81), Carlson and his associates (59), and others (310, 312) have reported upon the effective use of this agent in various phases of anesthesiology.

See table 52 for a summary of the relaxing agents.

GENERAL COMMENTS ON RELAXING AGENTS

The introduction of the use of curare or intocostrin in conjunction with cyclopropane anesthesia by Griffith and Johnson (126, 127) in 1942 stands out as a very great landmark in the field of anesthesiology. The combined use of a relaxing agent and a general anesthetic presents certain advantages to the patient and to the surgeon. From the patient's point of view it permits an operative procedure to be carried out with a much smaller concentration or dose of the anesthetic than would otherwise be possible (144). From the surgeon's point of view it permits

found in ten subjects after the intravenous administration of 1,000 mgm. of this drug in a period of ten minutes that apnea lasted from eight to forty minutes with twenty minutes as an average. *In approximately ten to twelve per cent of patients that receive a large dose of succinylcholine over a relatively long* period of time, there is a prolongation of the respiratory depressant effect to a much greater extent than one would expect. Martin, Nowill, and Stephen (202), as well as Davis, Ellis and their associates (81), have written upon this subject. Neither group has found a satisfactory explanation of this occasional prolongation in the duration of the effect, nor has either of the groups been able to find a mechanism by which this effect may be terminated.

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adequate or total relaxation as desirable on thirty seconds' notice without increasing the dose of the anesthetic agent. This combination is particularly satisfactory with cyclopropane and a relaxing agent and particularly with cyclopropane and succinylcholine, in that with cyclopropane in concentrations which produce adequate relaxation, there may arise cardiac and cardiovascular effects that are undesirable; whereas with the addition of the small amount of succinylcholine, adequate relaxation can be produced under minimal doses of cyclopropane. It is hoped that by the judicious use of the anesthetic agent combined with the relaxing agent that the public health problem of anesthetic deaths as reported in detail by Beecher and Todd (15) in 1954 can be reduced to a bare minimum. This judicious use of the relaxing agents, however, demands that the individual using these agents be prepared at all times to assist the respiratory effort of the individual or to take it over completely. This in turn requires that the individual have a close-fitting mask available in use, or better I think to have an endotracheal tube in place so that he can adequately maintain the patient's gaseous exchange. This is particularly desirable in relation to relaxing agents and cyclopropane anesthesia where it has long been known that cyclopropane anesthesia alone depresses the respiratory activity to such an extent that unless it is augmented by the anesthesiologist, there will be an accumulation of carbon dioxide which is oftentimes undesirable.

It seems to me that succinylcholine provides the anesthesiologist with a most satisfactory agent from the production of relaxation. It might be considered an agent that approaches the ideal relaxing agent. This conclusion is based upon many factors. The most important and more readily observed are: first, the rapidity of onset of action once the drug is given intravenously; second, the rapidity with which the action of the drug is terminated after its effect has been produced, the onset of maximum effect requiring approximately thirty seconds and that of recovery from a full relaxing dose of one to five to eight minutes—

TABLE 52

Summary of relaxing agents

	Equivalent Doses	Onset of Maximal Effect	Duration of Action	Effect on System other Than N-M	Destruction or Excretion	Mode of Action	Pharmacologic Antagonists	References to Development of and Early Clinical Use
	mgm							
d-Tubo curarine chloride	7–16	1–2′	25–30′	Histamine release	30% in urine	Comp Block Ac Ch	Eserine Neostig Tensilon	King, 1935 Bennett, 1939 Griffith, 1942
Dimethyl-d Tubo curarine bromide	4–7	1′	20′	Histamine release	—	" "	Tensilon	Wilson, 1950
Flaxedil (gallamine triethyl iodide)	47–110	1–2′	20′	Dep vagus	30–100% in urine	" "	Tensilon	Bovet, 1947 Mushin, 1949
Laudolissin	12	4′	30–50′	Histamine release	?	" "	Tensilon	Collier and Taylor, 1949 Boderman, 1952
Mytolon	12	2–3′	15–20′	Salivary stimulation, bradycardia	80% in urine	Comp. and *depol*	Tensilon Weak	Hoppe, 1950 Arrowood, 1951
Syncurine (decamethonium bromide)	2–2.5	1–2′	20′	0	?	Depol.	No	Barlow and Ing, 1949 Paton and Zamis, 1949 Organe, 1949
Succinylcholine (diacetylcholine Cl)	20–40	30″	3–5′	0	Hydrolysis	Depol.	No	Hunt and Taveau, 1906 Bovet, 1949, DeBeer, 1949 Foldes, Little, Hampton, 1952

12

Explosive Hazards and Explosions with Cyclopropane

Cyclopropane, like the other inhalation anesthetic agents except nitrous oxide and chloroform, is explosive when diluted with air or oxygen over the range of concentrations which are necessary for anesthesia. Jones (161) has made careful studies of the explosive properties of different anesthetic agents including the upper and lower limits of inflammability in both air and oxygen mixtures as well as the minimum ignition temperatures in air and oxygen. Data taken from his report are given in table 6, page 14. The range of inflammable concentrations of cyclopropane in air and oxygen is slightly less than that of diethyl ether, but the anesthetic concentrations of each agent fall within the inflammable limits. The minimum ignition temperature for an ether-air mixture is 304°C., whereas that for cyclopropane-air is 498°C.

The explosive hazards of cyclopropane must be kept in mind when it is used and precautions taken to reduce these hazards.

These precautionary measures may be divided into two groups: First, the forbidding of the use of electrical apparatus or open flame in the operating room when cyclopropane or other inflammable agents are in use, such as electric motors for various uses, particularly for suction-pressure apparatus, x-ray and fluoroscope, high-frequency machines, cautery, and so forth; the fact that relatively few explosions with cyclopropane have been attributed to the use of electrical apparatus in the operating room indicates that the operating team has used care in this regard. Second, the prevention of the electrostatic charge and spark; explosions due to the sudden release of static charges are

thus it is very flexible, third, the ability to use the drug for single injection or continuous or intermittent drip to produce total relaxation for the duration of one to three minutes upon single injection, or satisfactory relaxation for periods of hours upon continuous or intermittent injection.

Two cases involved ether-O_2 and caused death of 1 patient by lung injury and slight injuries to several members of the operating room staff. Four cases involved ether-N_2O-O_2 and caused the death of 2 patients by lung injury, burns of the head of another patient, and slight burns of an anesthetist and 2 by-standers. One case involved ethylene-O_2 and this patient died of a ruptured lung. Three cases involved cyclopropane-O_2 and caused the death of 2 patients with ruptured lungs. One case involved an unknown combustible agent mixed with N_2O-O_2 and caused a moderately serious burn of the face of the patient.

4. Actual cautery. Twenty-two cases, total. Six cases involved ether-air and caused death of 1 patient with lung injury, and burns of 2 by-standers. Three cases involved ether-O_2 and caused death of 1 patient with lung injury. One case involved cyclopropane-O_2—no injuries. One case involved ethyl chloride-air—no injuries. Six cases involved ether-N_2O-O_2 and caused the death of 2 patients and slight injuries to 3 persons. One of these 4 cases also contained ether and N_2O; this case caused only slight injury to the anesthetist. One case involved acetylene-O_2 and caused slight injury of the patient.

5. Electrostatic sparks. Sixty-six cases, total. Five cases involving ether-air—no injuries. Six cases involving ether-O_2 and caused severe burns of 1 patient and slight injuries to 2 anesthetists and 1 by-stander. Fifteen cases involving ether-N_2O-O_2 and caused death of 1 patient by lung injury; bilateral lung injury in another patient who recovered; death of anesthetist by burns; and 4 patients suffered contused eyelids and other slight facial injury. One case involving ethylene-air—no injuries. One case involved ethylene-N_2O—anesthetist killed by bursting of tank and attendant maimed. Twenty-four cases involving ethylene-O_2 and caused 4 patients to die of lung injury (3 of these were also getting ether), 3 anesthetists moderately seriously injured; and 3 anesthetists and 2 by-standers slightly injured. Fourteen cases involving cyclopropane-O_2 and caused death of 6 patients by lung injury (2 of these were also getting ether-N_2O), 1 patient possibly suffered

more difficult to prevent than those from electrical apparatus. The custom of having a relatively high humidity, 60 per cent or more, in the operating room is undoubtedly of value since the moisture tends to prevent the building up of electrostatic charges. The humidity in the anesthetic system will soon reach a high level as rebreathing continues, but for safety one should rinse the bag with water before the gases are run into it.

Considerable work is being done at the present in an attempt to develop apparatus or equipment which may be used in the operating room to prevent the electrostatic explosions with cyclopropane; this work has not progressed sufficiently for the acceptance of any set of equipment over another (67).

EXPLOSIONS UNDER CYCLOPROPANE

The Committee of Fires and Explosions of The American Society of Anesthetists (67) has published a brief report of its study of explosions. The report covers 170 cases of fires or explosions under different anesthetic agents. Cyclopropane was the anesthetic in use in 21 of the total 170. The summary of this report is given below, as well as an excerpt from the discussion of the committee.

Summary of Anesthetic Explosions and Fires

1. Suction-pressure machine-spark in switch or motor of machines of many different manufacturers Thirty-nine cases. Thirty-eight involved ether-air and 1 cyclopropane-O_2. One person died and 4 were injured. No injury in cyclopropane case.

2. X-ray fluoroscopes. Eight cases, total. Four cases involved ether-air mixtures and caused no injuries. Three cases involved ether-N_2O-O_2 mixtures and caused death of 1 patient by pulmonary injury, and facial injury to 2 patients who recovered fully. One case involved cyclopropane-O_2 and caused slight injury to patient and anesthetist.

3. High-frequency machines (medical and surgical). Thirteen cases, total. Two cases involved ether-air and caused no injuries.

12. Faulty electrical wall plug. One case involving ether-N_2O-O_2 causing severe burns of face and extremities of surgeon and anesthetist.

13. Miscellaneous (including cases too vaguely described to be classified with the above groups). Fourteen cases, total. One case involving rapid release of large tank of ethylene with ignition of gas at valve outlet causing slight burn of attendant. Six cases involving ether-air or O_2 ignited by spark in some form of electrical apparatus; five cases failed to report as to injuries; one case caused patient severe head burns, surgeon severe leg and hand burns and nurse slight burn. Five cases involving ether-air or O_2 ignited by spark resulting from "faulty wiring". No report as to injuries given. Two cases involving ether-air—cause of ignition and injuries not stated.

The very great majority of anesthesia explosions and fires and fatalities due to these have been preventable, and probably will be prevented by the raising of the standards of education and practice of anesthesiology. The most common cause of the great majority of anesthesia fires and explosions has been due to ignorance of the general principles of basic medical science involved in the administration of modern anesthetics.

Comments relative to two or three points in the summary quoted above are desirable: First, that out of 99 accidents (groups 1, 2, 3, 4, 6, 7, 10) which could have been prevented by careful application of our present information, only five occurred while cyclopropane was being administered; this would indicate that a considerable amount of caution has been used with the simultaneous administration of cyclopropane and the use of special electrical apparatus. Second, that of 66 accidents due to electrostatic spark, cyclopropane was the agent in 14 cases. Third, the percentage of fatalities in the explosions with cyclopropane is much higher than with the other agents. These fatalities were due, as a rule, to the rupture of the lungs; this may be due to one of two or a combination of two factors, that a mixture of cyclopropane and oxygen explodes with a greater force than the other agents or that, due to the use of a closed system while administer-

lung injury (died 8 days later of advanced pulmonary tbc and pneumonia); 2 patients suffered lung injuries but fully recovered; 3 anesthetists and several by-standers slightly injured.

6. Cigarettes or matches. Five cases, total. Three cases involving oxygen therapy equipment and causing death of 2 patients, severe burns of 1 patient and slight burns of 2 patients. One case involving ether-air—no injuries. One case involving ethylene-acetylene-O_2!—no injuries.

7. Open flame. Seven cases, total. One case involving ether-air—no injuries. One case involving ether-O_2 causing death of patient. Three cases involving ether-N_2O-O_2—no injuries. One case involving ethylene-O_2 causing slight burns of dentist, 2 assistants and patient. One case involving an unstated anesthetic causing death of the patient by lung rupture.

8. Endoscopic instruments. Four cases, total. One case involving ether-air causing pharyngeal burn of patient who recovered fully. One case involving ether-air or -oxygen causing death of patient by lung injury and facial burn of surgeon. One case involving ethylene-O_2—injuries not stated. One case involving cyclopropane-O_2—no injuries.

9. Pressure explosions due to sudden release of tank pressure into anesthetic machines not bearing safety valves. Six cases, total. Four cases involving oxygen causing laceration of face of patient. One case involving carbogen causing laceration of arms of anesthetist. One case involving nitrous oxide causing no injuries.

10. Fires caused by ignition of combustible agent used for surgical field preparation. Five cases, total. Five cases involving alcohol or alcoholic solution, two were ignited by cautery causing one patient second degree burns of lips and cheek, two were ignited by surgical diathermy causing death of 1 patient by burns. One case involving ether causing the death of patient by burns.

11. Oxygen-oil combustions. Two cases, total. One case involving a broken gauge with oil in line causing slight burn of face of anesthetist. One case involving an oil-containing leather washer—no injuries.

type of source of ignition between the American cases and those of the British is due to the difference in time of 1935 to 1938, and around 1950, or whether it is due to increased measures to eliminate actual spark other than static, one cannot say as there is no recent report in the American literature covering recent series of explosions.

Considerable work has been done during the past ten to fifteen years in an effort to develop a non-explosive inhalation anesthetic agent that could be used safely to supplant the explosive agents like ether, ethylene, divinyl ether and cyclopropane.

We (268) have reported on the study of a long series of fluoranated and halogenated hydrocarbons as possible anesthetic agents in the animal. As a result of our studies, several were found that were satisfactory in producing anesthesia rapidly, but all produced a fall in the blood pressure during the deeper phases of anesthesia in the animal.

Raventos (263) and Johnstone (160) have reported their studies on the use of fluothane in anesthesia in animals and in man, respectively. This substance has many of the attributes of a satisfactory non-explosive inhalation anesthetic agent, and preliminary or early reports showed it to be a very satisfactory drug. More recently, however, reports of undesirable reactions in the patients, particularly in relation to cardiac arrhythmias and significant falls in blood pressure during anesthesia, are making its use as a safe anesthetic less probable. (351, 352, 353)

Thus it will be necessary for us to use the greatest caution in relation to those methods by which the hazards of explosion during the use of the explosive agents will be reduced to an absolute minimum. Except for the explosive hazard of cyclopropane, and these may be prevented entirely by proper application of our present knowledge as stated by Greene in 1941, it is the most satisfactory and most maneuverable of the inhalation anesthetic agents in use at the present time.

The greatest need of the anesthetist at the present time for the safe administration of cyclopropane is a simple and efficient system or apparatus which will prevent the risk of explosions.

ing cyclopropane and oxygen, the pressure built up in the anesthetic-respiratory system is greater than when open technic is used.

Greene (115) in 1941 wrote on the hazard of fire and explosion in anesthesia and reported an investigation of 230 cases in which there were thirty-six fatalities. In his analysis of the causes of the explosions, he found that the use of the x-ray apparatus, the cautery, the diathermy, suction-pressure machines, and endoscopic apparatus, all of which may have an open spark, were the causative agents in 161 of the explosions, whereas static electricity was ruled the causative agent in only sixty-three. The major agents in use for the anesthesia at the time the explosion occurred were ether in 141 instances, ethylene in 38 instances, and cyclopropane in 22 instances. Although cyclopropane was in use in approximately nine per cent of the explosions, death as a result of the explosion under cyclopropane accounted for about twenty-two per cent of the total. In the summary it is stated that seventy per cent of the explosions and sixty per cent of the deaths of patients were caused by igniting agents other than static, and these were completely preventable by measures known at the time of their occurrence. The sixty-three explosions ignited by static electricity might have been prevented because in no case were there in use all of the safeguards which were known and recommended by competent authorities at the time of the explosions.

The most recent report on the explosive hazards of anesthetic agents is that called "The Working Party on Anesthetic Explosions" by the Ministry of Health, London, 1956, with Professor Gilbert Stead (311) as the chairman. This report covers the period of 1947 through 1953 Cyclopropane was used as the main anesthetic agent in twelve of these accidents, ether being the main anesthetic agent in eighteen of the accidents. The probable source of ignition in this series is the exact reverse of that in the two previous series mentioned in that static spark accounted for over sixty per cent of the ignition sources, whereas electric heater, diathermy, switch, etc. accounted for less than thirty-eight per cent of the sources of the ignition. Whether this difference in the

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